In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Case No. 10-394V

Filed: February 1, 2017

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LAURA OLIVER and EDDIE OLIVER, JR., Parents and Legal Representatives of E.O., III,	Chief Special Master Dorsey
Petitioners,	Ruling on the Record; Entitlement; SCN1A Gene Mutation; Severe Myoclonic Epilepsy of Infancy ("SMEI"); Dravet Syndrome; Chronic Complex Partial Seizure Disorder; Diphtheria-Tetanus-acellular Pertussis ("DTaP"); Hepatitis B ("Hep B"); Inactivated Poliovirus ("IPV"); Pneumococcal Conjugate ("PCV"); Rotavirus Vaccines.
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
* * * * * * * * * * * * * * *	

Clifford J. Shoemaker, Shoemaker and Associates, Vienna, VA, for petitioners.
Lara A. Englund, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On June 25, 2010, Laura Oliver and Eddie Oliver, Jr. ("petitioners"), filed a petition for compensation on behalf of their son, E.O. III ("E.O."), under the National Vaccine Injury Compensation Program ("the Program" or the "Vaccine Act").[2] Petitioners alleged that E.O. developed a fever and febrile seizures, that he continued to experience seizures, and that he

[1] Because this decision contains a reasoned explanation for the undersigned's action in this case, the undersigned intends to post this ruling on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012)(Federal Management and Promotion of Electronic Government Services). As provided by Vaccine Rule 18(b), 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).

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

ultimately developed a chronic complex partial seizure disorder as a result of receiving the Diphtheria-Tetanus-acellular Pertussis ("DTaP"), Hepatitis B ("Hep B"), Inactivated Poliovirus ("IPV"), Pneumococcal conjugate ("PCV"), and Rotavirus vaccines on April 9, 2009. See Petition (ECF No. 1) at ¶¶ 5, 6. Respondent recommended against awarding compensation to petitioners. See Respondent's Report ("Resp's Rep.") dated July 29, 2011 (ECF No. 40) at 15.

Medical records reflect that E.O. was born with a mutation of his SCN1A gene and that he has a seizure disorder known as Dravet syndrome. To date, there have been at least 15 other Program cases which involved children with SCN1A mutations, and compensation has been denied in all of these cases.[3] As in the other cases, petitioners' expert opines that the SCN1A mutation made E.O. susceptible to developing Dravet syndrome, that a gene-environmental interaction is at play, and that the vaccinations trigger that interaction. Respondent asserts that E.O.'s mutation is the sole cause of his Dravet syndrome and his resulting neurological condition.

The undersigned agrees with respondent that E.O.'s SCN1A gene mutation is the reason that he has Dravet syndrome and its associated neurological condition and finds that petitioners have failed to show by preponderant evidence that E.O.'s injuries were caused by his April 9, 2009 vaccinations. Although E.O.'s vaccinations may have caused a fever or otherwise triggered

[3] Faoro v. Sec'y of Health & Human Servs., 10-704V, 2016 WL 675491 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), review denied 128 Fed. Cl. 61 (2016); Barclay ex rel. Ramirez v. Sec'y of Health & Human Servs., 07-605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014); review denied 122 Fed. Cl. 189 (2015); Santini et al. v. Sec'y of Health & Human Servs., 06-725V, 2014 WL 7891507 (Fed. Cl. Spec. Mstr. Dec. 15, 2014); review denied 122 Fed. Cl. 102 (2015); Waters v. Sec'y of Health & Human Servs., 15-320V, 2015 WL 3898079 (Fed. Cl. Spec. Mstr. June 4, 2015); Mathis v. Sec'y of Health & Human Servs., 09-467V, 2014 WL 3955650 (Fed. Cl. Spec. Mstr. July 24, 2014); McHerron v. Sec'y of Health & Human Servs., 07-753V, 2014 WL 3360324 (Fed. Cl. Spec. Mstr. June 18, 2014); Barnette v. Sec'y of Health & Human Servs., 06-868V, 2012 WL 5285414 (Fed. Cl. Spec. Mstr. Sept. 26, 2012); aff'd 110 Fed. Cl. 34 (2013); Deribeaux v. Sec'y of Health & Human Servs., 05-306V, 2011 WL 6935504 (Fed. Cl. Spec. Mstr. Dec. 9, 2011); aff'd 105 Fed. Cl. 583 (2012); aff'd 717 F. 3d 1363 (Fed. Cir. 2013); Snyder et al. v. Sec'y of Health & Human Servs., 07-59V, 2011 WL 3022544 (Fed. Cl. Spec. Mstr. May 27, 2011); rev'd 102 Fed. Cl. 305 (2011); reinstated 553 F.App'x. 994 (Fed. Cir. 2014); Harris v. Sec'y of Health & Human Servs., 07-60V, 2011 WL 2446321 (Fed. Cl. Spec. Mstr. May 27, 2011); rev'd 102 Fed. Cl. 282 (2011); reinstated 553 F. App'x. 994 (Fed. Cl. 2014); Hammitt v. Sec'y of Health & Human Servs., 07-170V, 2011 WL 1135878 (Fed Cl. Spec. Mstr. March 4, 2011); review denied 98 Fed. Cl. 719 (2011); aff'd 676 F.3d 1373 (Fed. Cir. 2012); Sucher v. Sec'y of Health & Human Servs., 07-58V, 2010 WL 1370627 (Fed. Cl. Spec. Mstr. March 15, 2010); Stone v. Sec'y of Health & Human Servs., 04-1041V, 2010 WL 1848220 (Fed. Cl. Spec. Mstr. Apr. 15, 2010); rev'd 95 Fed. Cl. 233 (2010); remanded 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011); review denied 99 Fed. Cl. 187 (2011); aff'd 676 F.3d 1373 (Fed. Cir. 2012); rehearing denied 690 F.3d 1380 (2012); cert. denied 133 S. Ct. 2022 (2013); Schniegenberg v. Sec'y of Health & Human Servs., 13-347V, 2014 WL 4674382 (Fed. Cl. Spec. Mstr. Apr. 29, 2014); Craner v. Sec'y of Health & Human Servs., 10-475V, 2011 WL 6401290 (Fed. Cl. Spec. Mstr. Oct. 27, 2011).

his first seizure, neither that initial seizure nor his vaccinations caused his Dravet syndrome or neurological complications. For that reason, the undersigned also finds that respondent has provided preponderant evidence of an alternative cause of E.O.'s injuries, and, therefore, petitioners are not entitled to compensation.

I. Procedural History

Petitioners filed a petition on June 25, 2010, alleging that the DTaP, Hep B, IPV, PCV, and Rotavirus vaccinations that E.O. received on April 9, 2009, caused him to develop "a fever and febrile seizures . . . [and] a chronic complex partial seizure disorder." Petition at ¶¶ 5, 6. Over the next nine months, petitioners filed medical records, and on March 16, 2011, petitioners filed a statement of completion. See Petitioners' Exhibits ("Pet'rs' Exs.") 1-19; Statement of Completion dated March 16, 2011. At a status conference on April 6, 2011, respondent identified additional records related to the genetic testing of E.O. and his parents. See Order dated April 19, 2011 (ECF No. 29) at 1. Over the next three months, petitioners filed records of E.O.'s genetic test results, neuropsychological evaluation, occupational and speech evaluations, Emergency Medical Services ("EMS") reports, and updated medical records from E.O.'s pediatric neurologist, Dr. James Wheless. See Pet'rs' Exs. 20-26 (ECF Nos. 30-31, 34, 39).

On July 29, 2011, respondent filed her Rule 4(c) Report, recommending against compensation. Resp's Rep. at 1. Respondent stated that petitioners did not allege that E.O. suffered an injury listed on the Vaccine Injury Table, nor did they establish causation in fact by a preponderance of the evidence. Id. at 13. Respondent further noted from E.O.'s medical records that "he had tested positive for SCN1A gene defect (borderline SMEI syndrome),"[4] and that "[E.O.'s] own treating neurologist, Dr. Wheless, has attributed [E.O.'s] seizure disorder not to the vaccines, but to a mutation in his SCN1A gene." Id. at 10-11, 14 (citing Pet'rs' Ex. 9 at 37; Pet'rs' Ex. 18 at 26, 28).

On April 16, 2012, petitioners filed an expert report from Dr. Yuval Shafrir. See Pet'rs' Ex. 28. In addition to the expert report, petitioners filed Dr. Shafrir's curriculum vitae and 17 medical articles referenced in his report. See Pet'rs' Exs. 29-46. Dr. Shafrir agreed with Dr. Wheless that E.O.'s condition is "very reminiscent of Dravet syndrome." See Pet'rs' Ex. 28 at 11. However, he argued that medical literature has shown an association between Diphtheria-Tetanus-Pertussis ("DPT") vaccination and the onset of Dravet syndrome. See id. at 13.

On December 17, 2012, respondent filed expert reports from Dr. Gerald Raymond and Dr. Rajesh Sachdeo, along with their curricula vitae and medical literature. See Resp's Exs. A-D. Dr. Raymond and Dr. Sachdeo both opined that E.O.'s SCN1A gene mutation, rather than the vaccines, was more likely the cause of his Dravet syndrome. Resp's Ex. A at 8, 11-12; Resp.'s Ex. C at 1. On March 14, 2014, and August 8, 2014, petitioners filed two supplemental expert reports from Dr. Shafrir. Pet'rs' Exs 47, 68. Respondent filed a supplemental expert report from Dr. Raymond on September 22, 2014. Resp's Ex. E.

[4] Severe Myoclonic Epilepsy of Infancy ("SMEI") is also known as Dravet syndrome. See Section II(C), infra, for a more complete description.

On September 22, 2014, respondent filed a motion for a ruling on the record, recommending dismissal of the case on the basis of the written record without an evidentiary hearing. Resp's Motion for a Ruling on the Record ("Resp's Mot.") dated September 22, 2014 (ECF No. 93) at 13. Respondent argued that the claim should be dismissed, because petitioners failed to distinguish their case from previously dismissed SCN1A cases[5] with the same experts and medical theory. Id. at 13-14. On December 9, 2014, petitioners filed their third and fourth supplemental expert reports from Dr. Shafrir, along with additional medical literature. Pet'rs' Exs 74-80. On the same day, petitioners also filed a response to respondent's motion, indicating that E.O.'s case included new evidence that was not presented in the prior SCN1A cases. Pet'rs' Response to Resp's Mot. (ECF No. 99) at 2 n.2. Further, petitioners claimed that precluding them from presenting their theory of causation simply because they used the same expert as prior SCN1A cases would become a "dangerous precedent." Id. at 5.

On January 17, 2015, respondent filed a reply to petitioners' response. See Resp's Reply dated January 7, 2015 ("Resp's Reply") (ECF No. 101). Respondent clarified that she was not arguing that petitioners' theory of causation is precluded. Id. at 1. Rather, respondent reiterated that petitioners failed to establish causation in fact by preponderant evidence and that the written record should be adequate for the undersigned to dismiss the case without an evidentiary hearing. Id. at 1.

During a status conference on March 3, 2015, the undersigned denied respondent's motion for a ruling on the record because, at the time, it was unclear whether E.O.'s specific SCN1A gene mutation was pathogenic. Specifically, his mutation was described as "a variant of 'unknown significance,' and [it had not yet] been described in the literature." Order dated March 3, 2015 (ECF No. 102) at 1. The undersigned sought more information about the mutation and requested that petitioners submit E.O.'s updated pediatric neurological records, his parents' genetic testing results, and an evaluation from his genetic specialist. Id. at 2. She also ordered both parties to submit supplemental expert reports. Id. In accordance with the undersigned's March 3, 2015 Order, petitioners filed additional medical records, three supplemental expert reports from Dr. Shafrir, and medical literature. Pet'rs' Ex. 81-135. Respondent filed a second supplemental expert report from Dr. Raymond. Resp's Ex. F.

On September 22, 2015, after reviewing the additional records and expert reports, the undersigned held a status conference to discuss her thoughts on the resolution of this case. See Order dated September 22, 2015 (ECF No. 113). Subsequently, on March 28, 2016, petitioners filed a motion for a ruling on the record. Pet'rs' Motion for a Ruling on the Record dated March 28, 2016 ("Pet'rs' Mot.") (ECF No. 126). Respondent filed a responsive brief on May 31, 2016. Resp's Response to Pet'rs' Mot. dated May 31, 2016 ("Resp's Resp.") (ECF No. 127) at 1. On

[5] See Resp's Mot. at 10-13 (citing Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373 (Fed. Cir. 2012); Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363 (Fed. Cir. 2013); Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994 (Fed. Cir. 2014); Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34 (2013); Waters v. Sec'y of Health & Human Servs., No. 08-76V, 2014 WL 300936 (Fed. Cl. Spec. Mstr. Jan. 7, 2014)).

July 15, 2016, petitioners filed a reply to respondent's response. Pet'rs' Reply dated July 15, 2016 (ECF No. 128) at 2.

This matter is now ripe for adjudication on petitioners' motion for a ruling on the record.

II. Summary of Relevant Medical Records and Affidavit

A. Summary of Medical Records

E.O. was born on October 2, 2008, at St. Mary's Hospital in Athens, Georgia. Pet'rs' Ex. 16 at 34. He was delivered at 38 weeks of an uncomplicated pregnancy. See generally, Pet'rs' Exs. 7, 16. His birth weight was six pounds 14 ounces and his APGAR scores[6] were six and seven at one and five minutes, respectively. See Pet'rs' Ex. 16 at 34. E.O.'s neonatal course presented "respiratory distress and decreased pulses in the lower extremities." Id. at 46. E.O. was admitted to the special care nursery. Id. His initial condition was stabilized by dextrose intravenous ("IV") fluids, antibiotics, and an IV bolus of normal saline. Id. On October 4, 2008, E.O.'s physical examination was unremarkable except for jaundice, and he was discharged home. Id. at 47.

E.O. received his early pediatric care from Dr. Melissa Martin and Dr. Jeanne Martin. See generally, Pet'rs' Ex. 8. On April 9, 2009, E.O. saw Dr. Jeanne Martin for his six-month well-baby visit and vaccinations. Id. at 19. His temperature on examination was 97.4 degrees Fahrenheit. Id. Dr. Jeanne Martin reported that E.O. had normal growth and development as a six-month infant, despite his puffy right eye with clear drainage. Id. E.O. received DTaP, Hep B, IPV, PCV, and Rotavirus vaccinations during this visit. Id. at 3.

At approximately 11:30 that evening, Mrs. Oliver awoke to "repetitive grunting sounds through a baby monitor," and found E.O. seizing in his bed. Pet'rs' Ex. 15. She called 911, and EMS arrived at the Oliver home a few minutes later. Pet'rs' Ex. 26 at 3. Ms. Oliver stated that E.O.'s seizure lasted approximately four to five minutes. Id. The EMS caregiver reported that E.O. was "very sluggish and appear[ed] postictal . . . and [his] skin [was] very hot to [the] touch on [his] forehead as well as his trunk." Id. at 6.

At 12:19 a.m. on April 10, 2009, E.O. arrived at the Banks-Jackson-Commerce ("BJC") Medical Center. Id. He presented to the ER with "a fever of 101.3 degrees, red eyes with discharge from his right eye, and a runny nose." Id. at 5; Pet'rs' Ex. 1 at 13. E.O.'s parents reported to the ER physician, Dr. Michael Herron, that E.O. received vaccinations the previous day. Pet'rs' Ex. 1 at 13. On examination, Dr. Herron reported that E.O. was "happy, playful, smiling, and active in the ER." Id. After reviewing his blood test results and radiology report, Dr. Herron diagnosed E.O. with a febrile seizure. Id. at 16-19. Dr. Herron prescribed pediatric

[6] Appearance, Pulse, Grimace, Activity, and Respiration ("APGAR") score is a method of evaluating newborns to determine their overall health. See Nelson Textbook of Pediatrics (19th ed. 2011) at 536-37.

Tylenol and Motrin and discharged E.O. with instructions to follow up with his pediatrician. Id. at 19.

On April 10, 2009, E.O. was seen by his pediatrician, Dr. Jeanne Martin, for follow-up. See Pet'rs' Ex. 8 at 18. Dr. Martin that E.O. was "okay by the time he got to the hospital," and that his condition was normal on examination except for a tearing right eye. Id. His body temperature was stabilized at 97.1 with no fever. Id. Dr. Martin diagnosed E.O. with complex febrile seizure and conjunctivitis in the right eye. Id.

E.O. did not have any health issues or seizures for the next two months. See Pet'rs' Ex. 19 at 190, 198. On June 16, 2009, approximately two months after his six-month vaccinations, Mrs. Oliver noticed that E.O. was not moving his right side and did not interact with her for about ten minutes. Id. at 192. She took him to the ER of St. Mary's Hospital. Id. at 190. The ER nurse, Roberta Walters, reported E.O.'s level of consciousness as "awake and alert." Id. at 191. The result of his brain CT scan was normal. Id. at 206. The ER physician, Dr. Rick Brewer, diagnosed E.O. with a "possible seizure" and discharged him in a stable condition. Id. at 190. Dr. Brewer ordered an EEG[7] test for E.O. and instructed petitioners to follow up with Dr. Elizabeth Sekul at the Medical College of Georgia ("MCG"). Id. at 196, 202. The EEG results were "mildly normal for age because of asymmetrical slowing over the left hemisphere." Id. at 182. Although nonspecific for E.O.'s age, the EEG specialist concluded that such a finding "may reflect interictal seizure in the left hemisphere." Id.

On June 18, 2009, E.O. was seen by Dr. Elizabeth Sekul, a pediatric neurologist at MCG. Pet'rs' Ex. 4 at 84-87. On examination, Dr. Sekul described E.O. as "alert, playful, interactive, very socially engaging . . . [and] in no apparent distress." Id. at 85. In a response letter to Dr. Brewer, Dr. Sekul reported that E.O. had "normal development [and] has had two events." Id. at 86. Dr. Sekul stated that the first event was "associated with his immunization," and "the second event was only some transient hemiparesis, most likely secondary to a Todd."[8] Id. He also reported that E.O.'s EEG results from St. Mary's Hospital showed "no epileptiform discharges" in the left hemisphere and "this would have been consistent with possible Todd's." Id. Dr. Sekul planned to order an MRI to exclude stroke-like changes and a repeat EEG to ensure that the left hemisphere was normalized. Id. The repeat EEG was normal. Id. After reviewing E.O.'s medication history of Diastat 2.5 mg, Dr. Sekul prescribed Trileptal and discharged him home. Id.

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[7] An electroencephalogram ("EEG") is a diagnostic test that records "the potentials on the skull generated by currents emanating spontaneously from nerve cells in the brain," which "correlate well with different neurologic conditions." Dorland's Illustrated Medical Dictionary ("Dorland's") (32d ed. (2012)) at 602.

[8] "Todd's paralysis is a neurological condition experienced by individuals with epilepsy, in which an epileptic seizure is followed by hemiparesis or monopoiesis lasting for a few minutes or hours, or occasionally for several days." Dorland's at 1378. Hemiparesis is defined as "paralysis of the lower half of one side of the body." Id. at 837. Monopoiesis means "paresthesia on a single limb." Id. at 1178.

Over the summer, E.O. had several seizures, all resulting in ER visits. See Pet'rs' Ex. 19 at 168; Pet'rs' Ex. 5 at 3; Pet'rs' Ex. 19 at 153. On August 17, 2009, at approximately 10 months of age, E.O. was evaluated by Dr. Jun Park, a pediatric neurologist in Atlanta, Georgia. See Pet'rs' Ex. 2 at 5-6. Dr. Park reported that E.O. had a total of six "sporadic" seizures, with the first event "at six months of age on the night after the six-month vaccination," and the last event on the previous Wednesday. Id. at 5. Dr. Park documented that E.O.'s head CT scan, brain MRI, EEG, and repeat EEG were reportedly normal. Id. Dr. Park also emphasized that E.O. had "normal developmental milestones." Id. Dr. Park diagnosed E.O. with focal epilepsy. Id. He ordered a repeat EEG, which was normal and showed "no focal features or epileptiform discharges." Id. at 2. Dr. Park prescribed Diastat for the first time and instructed petitioners to follow up in six weeks. Id. at 6.

Beginning in March 2010, E.O. began to have prolonged seizures, all of which resulted in ER visits. See Pet'rs' Ex. 3 at 2-8; Pet'rs' Ex. 4 at 5-6, 15-24, 33-34, 54-56, 71-72. On March 1, 2010, E.O. had a seizure that lasted about three hours, and he was admitted to the pediatric intensive care unit ("ICU") at MCG. Pet'rs' Ex. 4 at 54-70. Dr. Suzanne Strickland diagnosed him with "complex partial seizures" and prescribed Keppra 250 mg, Trileptal 240 mg, and Diastat 7.5 mg. Id. at 54-56. During another ER visit on March 8, 2010, Dr. Strickland reported that E.O. continued to have "daily seizures" and "the episodes have become progressively worse with increase in duration as well as frequency." Dr. Strickland updated his prescriptions to include Keppra 300 mg, Dilantin 25 mg, and Diastat 7.5 mg. Id. at 33-35. On April 9, 2010, E.O. returned to the ER at MCG after a prolonged seizure that lasted forty-five minutes. Id. at 18. During this episode, Dr. Strickland reported that E.O. did not respond to Diastat. Id. at 16. E.O. did not become stabilized to baseline until given two doses of Ativan 1 mg. Id. at 3, 24. Upon discharge, he developed additional seizure activities and required extra doses of Diastat and Dilantin. Pet'rs' Ex. 4 at 3. On April 24, 2010, Dr. Park diagnosed E.O. with "intractable epilepsy from possible left frontal epileptic foci." Id. at 4. Dr. Park prescribed Keppra 3.5 mL, Klonopin 0.5 mg, Dilantin 25/25/50 mg, and Diastat 7.5 mg. Id.

On April 26, 2010, E.O. was referred to Dr. James Wheless, a pediatric neurologist at LeBonheur Children's Medical Center ("LeBonheur") in Memphis, Tennessee. See Pet'rs' Ex. 9 at 2. Dr. Wheless described E.O.'s seizures for the past two months as "characterized by brief cessation of his ongoing activity or brief pauses, with eye blink." Id. at 7. Dr. Wheless noted that E.O. had not adequately responded to Trileptal, Dilantin, Keppra, Klonopin, Ativan/Lorazepam, Topamax, Depakote, or ethosuximide. Id. at 7, 32. After a full diagnostic evaluation, Dr. Wheless diagnosed E.O. with "intractable, cryptogenic childhood absence epilepsy." Id. at 9. Despite being placed on numerous medications, E.O.'s seizures could not be controlled. Id. at 7, 32.

On June 1, 2010, E.O. returned to LeBonheur for further diagnostic testing. Pet'rs' Ex. 9 at 31. He tested positive for SCN1A gene defect. Id. at 36-37. E.O.'s parents also underwent genetic testing for SCN1A mutation and neither parent had the mutation. See Pet'rs' Ex. 18 at 26; Pet'rs' Ex. 23 at 2-8. During E.O.'s stay at the hospital, he had a prolonged seizure that lasted 50 minutes at the time of admission, but his condition improved after he was placed on a ketogenic diet. See Pet'rs' Ex. 9 at 37-38. On June 4, 2010, Dr. Wheless discharged E.O. with diagnosis of "intractable, symptomatic absence and partial new onset seizures of independent

hemisphere origin and episodes of status epilepticus," and "sodium channelopathy due to SCN1A gene defect." Id. at 37. He prescribed Carnitor 1.5 mL, Keppra 500mg, as well as a ketogenic diet plan with calcium and multivitamin supplements. Id. at 38.

On July 19, 2010, E.O. was seen by Dr. Wheless for follow-up. See Pet'rs' Ex. 18 at 25-27. E.O.'s mother reported that he continued to have frequent absence seizures, but that he only had one prolonged complex partial seizure on June 13, 2010. Id. at 26. E.O.'s developmental delay became apparent around this time. Id.; see also Resp's Ex. C at 4. Dr. Wheless performed a general physical exam, a neurologic exam, and a motor exam. Pet'rs' Ex. 18 at 26. The impression was "intractable, symptomatic childhood absence and complex partial seizures of independent hemisphere origin secondary to SCN1A gene defect (borderline SMEI syndrome)," and "encephalopathy characterized by speech delay." Id.

B. Affidavit from E.O.'s Mother

The record includes an affidavit from E.O.'s mother, Laura Oliver. See Pet'rs' Ex. 15 at ¶ 1. Mrs. Oliver stated that E.O. received his two-, four-, and six-month vaccinations at Dr. Jeanne Martin's office. Id. at ¶ 7. She reported that E.O. was healthy and developing normally prior to receipt of any vaccinations, and he had no noticeable reactions to his two- or four-month vaccinations except for a slight fever. Id. at ¶¶ 6, 8.

Mrs. Oliver stated that the night E.O. received his six-month vaccinations, she "awoke to repetitive grunting sounds through a baby monitor," and found E.O. "unconscious and unable to wake up." Id. at ¶ 9. She reported that "[E.O.] was convulsing in his entire body; [his] eyes rolled back in his head[,] and he turned blue." Id. Mrs. Oliver stated that her husband called 911 and an ambulance took them to the ER. Id. She reported that E.O.'s vitals dropped and his skin became blotchy on their way to the ER, which forced them to "make an emergency stop at a local hospital for immediate care." Id. She stated that the ambulance took them to the ER of BJC Medical Center, where E.O. was diagnosed with a febrile seizure. Id.

Mrs. Oliver also described E.O.'s second seizure episode, which resulted in another ER visit to St. Mary's Hospital. Id. at ¶ 10. She stated that "[E.O.] was found in his crib not moving one side of his body, and he had no neck control to hold his head up." Id. She stated that the ER physician diagnosed E.O. with Todd's paralysis as a result of a seizure and that Dr. Elizabeth Sekul, a pediatric neurologist, diagnosed E.O. with a complex partial seizure disorder. Id.

Mrs. Oliver reported that on March 1, 2010, E.O. had a "prolonged complex partial seizure of more than three hours," and was admitted to the ICU of MCG. Id. at ¶ 14. She also reported E.O.'s several prolonged seizures in June 2010. Id. at ¶ 15. Mrs. Oliver described that "there is no pattern to the frequency of [E.O.'s] seizures," and he continues to have "absence seizures all day long every few seconds." Id.

Mrs. Oliver stated that despite "more than 25 changes to dosages and medications" prescribed by MCG pediatric neurologists, E.O.'s seizures remained "uncontrolled in November 2010," and "continued to worsen." Id. at ¶¶ 11-12, 17. She reported that the length of his prolonged complex partial seizures fluctuated from a few seconds to more than three hours. Id.

at ¶ 11. In addition to medications, Mrs. Oliver stated that E.O. was administered sedatives several times during his testing procedures at MCG, including MRI, EEG, video EEG, and SPECT.[9] Id. at ¶ 12. She further reported that E.O. suffered serious side effects caused by medications and the strict ketogenic diet plan, including little growth, weight loss, restlessness during sleep, aggressive behaviors, stomach discomfort, and other problems. Id. at ¶ 19.

Mrs. Oliver's statement also highlighted the difficult impact of her son's disease on the family. Id. at ¶¶ 18, 20-21. She stated that E.O.'s uncontrolled symptoms and the frequent hospital visits forced her to take a leave from work, which in turn forced the family to seek other avenues of health insurance that could cover E.O.'s condition. Id. Fearing additional uncontrolled seizures, Mrs. Oliver described that the family is unable to take E.O. in public, to children's functions, or to relatives' residences where "an appropriate medical facility is not within a reasonable distance." Id. at ¶ 20.

C. Genetic Testing, SCN1A Mutation, and Dravet Syndrome

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

1. SCN1A Gene Mutation

On April 26, 2010, Dr. Yong Park at MCG referred E.O. to Dr. James Wheless, a pediatric neurologist at LeBonheur, for neurologic evaluation and treatment recommendations. See Pet'rs' Ex. 9 at 2. Dr. Wheless recommended a full diagnostic evaluation consisting of prolonged video EEG, brain MRI, SPECT, neuropsychological testing, occupational and speech assessments, and genetic studies. Id. at 5. On the same day, E.O. underwent genetic testing for SCN1A mutation. Id. at 31. On June 1, 2010, Athena Diagnosis, Inc. reported E.O.'s genetic test results, which identified "a DNA sequence variant" on his SCN1A gene.[10] See Pet'rs' Ex. 20 at 1. The significance of the mutation was characterized as "unclear or unknown." Id.

On June 4, 2010, Dr. Wheless diagnosed E.O. with "sodium channelopathy due to SCN1A gene defect," based upon the results of his genetic testing. See Pet'rs' Ex. 9 at 37. Based on the results of the genetic testing, Dr. Wheless recommended a new medication, Carnitor 1.5 mL, as well as the ketogenic diet plan with calcium and multivitamin supplements. Id. at 38.

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[9] The SPECT test is "single-photon emission computed tomography." Dorland's at 1742.

[10] Athena Diagnosis, Inc. reported E.O.'s test results as follows:
"SCN1A DNA Sequencing Variants:
SCN1A variant 1: 4 base pair deletion;
Nucleotide position: IVS1+4_IVS1+7;
DNA variant type: Variant of unknown significance.
No other abnormal DNA sequence variants were identified in the remainder of the coding sequence or intron/exon junctions of this gene." Pet'rs' Ex. 20 at 1.

E.O.'s parents also underwent genetic testing for SCN1A mutation and the results revealed that they do not have the mutation. Thus, E.O.'s mutation is de novo. See Pet'rs' Ex. 18 at 26; Pet'rs' Ex. 23 at 2-8.

The SCN1A gene encodes for a sodium channel, which is "a portion of a channel that allows the transport of sodium molecules across cell membranes in the neurons." Resp's Ex. A at 6-7. The flow of sodium molecules permits appropriate transmission of information from one cell to another. Id. at 6. SCN1A gene mutations affect neuron cells in various ways, depending on the particular mutation, and how the mutation affects the structure and function of the sodium channel. Id. So far, several neurological conditions have been associated with the SCN1A gene mutation, including familial hemiplegic migraines, several epilepsy syndromes, Generalized Epilepsy with Febrile Seizures plus ("GEFS+"), and E.O.'s condition, Dravet syndrome. Id. at 5-7.

There are several SCN1A databases reported in the literature. One is maintained by the Institute of Neuroscience at GuangZhou Medical University in Guangdong Province in China Pet'rs' Ex. 100 at 1 (citing database at http://www.gzneurosci.com/scn1adatabase/index.php) (last visited Jan. 23, 2017). "In this database, there [is a] mutation…which appears identical to the mutation of E.O." Id.; see also database entry No. 40. The child with the identical mutation was also reported to have Dravet syndrome. Resp's Ex. F at 2.

2. Dravet Syndrome

Dr. Wheless first diagnosed E.O. with borderline severe myoclonic epilepsy of infancy ("SMEI") syndrome in March 2010, when he was 21 months old. Pet'rs' Ex. 18 at 26. The diagnosis was based on the fact that E.O. showed signs of encephalopathy which were characterized by his speech delay. Id. At the time of diagnosis, it was also noted that E.O. suffered from "intractable, symptomatic childhood absence and complex partial seizures of independent hemisphere origin." Id. All of these symptoms are indicators of Dravet syndrome.

Dravet syndrome is an extremely rare syndrome with an incidence of one in 40,000 children. Pet'rs' Ex. 28 at 12; Pet'rs' Ex. 35 at 488.[11] Seventy to 80 percent of Dravet syndrome cases are caused by SCN1A mutations. Pet'rs' Ex. 35 at 488. Ninety percent of these mutations are de novo.[12] Id. The gene which is affected by the mutation is in the alpha subunit of the SCN1A gene, which "encodes the voltage-dependent sodium channel (Na_v 1.1)." Pet'rs' Ex. 64

[11] See Berkovic, Samuel, et al., "De-novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study," 5 LANCET NEUROL. 488-492 (2006) [Pet'rs' Ex. 35].

[12] 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 parents or in the fertilized egg itself." National Institutes of Health, "Genetics Home Reference," available at <http://ghr.nlm.nih.gov/glossary=denovomutation> (last visited Dec. 8, 2016).

at 1.[13] The SCN1A gene is "an important epilepsy-related sodium channel gene." Pet'rs' Ex. 48 at 9.[14] Research has shown that there is a "powerful network hyperexcitability underlying Dravet syndrome, a severe epilepsy of infancy." Id.

Dravet syndrome is also referred to as SMEI and is an epilepsy syndrome that starts at about six months of age. Pet'rs' Ex. 40 at 3.[15] The initial seizure may be accompanied by a fever. Id. Development is generally normal at the onset of the disease, but a subsequent and progressive decline in intellectual function often occurs. Id. The time frame in which the disease first presents overlaps with the schedule of routine childhood vaccinations. Id. at 2-3. Children with Dravet syndrome usually have clonic[16] seizures in the first year of life, followed by myoclonic[17] seizures. Pet'rs' Ex. 37 at 1. In addition to developmental delay, the children may have an ataxic[18] gait. Id.[19] The seizures are refractory to treatment. Id.

The clinical course of Dravet syndrome is "characterized by onset of recurrent febrile and/or afebrile hemiclonic or generalized seizures…. in a previously healthy infant." Pet'rs. Ex. 41 at 2.[20] The seizures usually evolve into multiple types of seizures which are drug resistant. Id. By the second year of life, children usually have an encephalopathy with cognitive, behavioral and developmental delays. Id.; Pet'rs' Ex. 55 at 2.[21] Even children with Dravet

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[13] Okumura, Akihisa, et al., "Acute Encephalopathy in Children with Dravet Syndrome," 53 EPILEPSIA 79-86 (2012) [Pet'rs' Ex. 64].

[14] Klassen, Tara, et al., "Exome Sequencing of Ion Channel Genes Reveals Complex Profiles Confounding Personal Risk Assessment in Epilepsy," 145 CELL 1036-48 (2011) [Pet'rs' Ex. 48].

[15] Tro-Baumann, Blanca, et al., "A Retrospective Study of the Relation Between Vaccination and Occurrence of Seizures in Dravet Syndrome, 52 EPILEPSIA 175-78 (2011) [Pet'rs' Ex. 40].

[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 "shock-like 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] Guerrini, Renzo, & Oguni, Hirokazu, "Borderline Dravet Syndrome: A Useful Diagnostic Category," 52 EPILEPSIA 10-12 (2011) [Pet'rs' Ex. 37].

[20] Catarino, Claudia, et al., "Dravet Syndrome as Epileptic Encephalopathy: Evidence from Long-Term Course and Neuropathology," 134 BRAIN 2982-3010 (2011) [Pet'rs' Ex. 41].
[21] Brunklaus, Andreas, et al., "Prognostic, Clinical and Demographic Features in SCN1A Mutation-Positive Dravet Syndrome," 135 BRAIN 2329-36 (2012) [Pet'rs' Ex. 55].

syndrome who have well controlled epilepsy experience developmental problems. Pet'rs' Ex. 55 at 4.

III. Standards for Adjudication

The Vaccine Act was established 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).

This Court is given jurisdiction to award compensation for claims where the medical records or medical opinion have demonstrated causation in fact by a preponderance of the evidence. See §§ 300aa-13(a)(1) and 11(c)(1)(C)(ii)(I). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must prove that that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccine's injury is "due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(B).

To receive compensation under the Program, petitioners must show either: (1) that E.O. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that E.O. suffered an injury that was actually caused by the vaccine (or vaccines) he received. See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006).

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

The causation theory must relate to the injury alleged. Thus, petitioners must provide a reputable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on their assertions. Rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 300aa-

13(a)(1). In determining whether petitioners are entitled to compensation, the undersigned shall consider all material contained in the record, § 300aa-13(b)(1), including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 300aa-13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' offered experts and rule in petitioners' favor when the evidence weighs in their favor. See Moberly, 592 F.3d at 1325-26 (holding that factfinders are expected and entitled to determine the reliability of the evidence presented to them and the credibility of the persons presenting that evidence"); Althen, 418 F.3d at 1280 (holding that "close calls" should be resolved in petitioner's favor).

Another important aspect of the causation-in-fact case law under the Program 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, 1302 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize the Daubert standard as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases.

IV. Issues to be Decided

As an initial matter, both parties agree that E.O. was born with a mutation of his SCN1A gene. Pet'rs' Memorandum ("Memo") dated March 28, 2016 (ECF No. 126) at ¶ 9; Resp's Resp. at 4-5. Thus, the parties agree that the vaccines did not cause the genetic mutation. See Pet'rs' Memo at ¶ 9. Rather, the parties dispute whether E.O.'s April 9, 2009 vaccinations can and did cause his seizure disorder, Dravet Syndrome, and resulting neurological condition. See Petition at ¶ 6; see also Pet'rs' Memo at ¶¶ 4, 34-35, 50. Secondly, the parties dispute whether E.O.'s vaccinations caused a significant aggravation of his condition. See Pet'rs' Memo at ¶ 56.

V. Expert Qualifications

In support of their claims, petitioners offer seven reports by Dr. Yuval Shafrir. See Pet'rs' Exs. 28, 47, 68, 74, 86, 100, 102. Respondent provides three reports by Dr. Gerald Raymond and one report by Dr. Rajesh Sachdeo. See Resp's Exs. A, C, E-F.

1. Petitioners' Expert, Dr. Yuval Shafrir

Dr. Yuval Shafrir is a pediatric neurologist at Sinai Hospital in Baltimore, Maryland. Pet'rs' Ex. 46 at 3. He attended Tel Aviv University Sackler School of Medicine in Israel during 1976-1982 and conducted his pediatric residency rotations in Israel. Id. at 1. After moving to the United States, he completed a pediatric residency at Cornell University Medical College. Id. Afterwards, Dr. Shafrir completed a fellowship in pediatric neurology at Washington University Medical Center in St. Louis and a second fellowship in pediatric neurophysiology and epileptology at Miami Children's Hospital. Id. Dr. Shafrir is board-certified in neurology with a specialty in pediatric neurology, clinical neurophysiology, and epilepsy. Id. at 2. In addition to his active private practice in pediatric neurology, Dr. Shafrir also served as an Assistant

Professor in Neurology and Pediatrics at multiple academic and medical institutions, including United Services University of the Health Sciences, Georgetown University School of Medicine, the University of Oklahoma School of Medicine, and most recently, the University of Maryland School of Medicine. Id. at 2-3. He has conducted numerous clinical studies in pediatric neurology and has published more than 20 peer-reviewed articles and abstracts. Id. at 3-6. Since 1991, he has been frequently invited to attend grand rounds and lectures across the country, as well as national and international academic annual meetings of pediatric neurology. Id. at 6-8.

2. Respondent's Expert, Dr. Gerald Raymond

Dr. Gerald Raymond is a pediatric neurologist who specializes in neuropathology and genetics. Resp's Ex. B at 1. He attended the University of Connecticut School of Medicine from 1980-1984. Id. After medical school, Dr. Raymond completed residency rotations in pediatrics and neurology at the Johns Hopkins Hospital and the Massachusetts General Hospital. Id. He then completed a fellowship in developmental neuropathology at Université Catholique de Louvain in Brussels, Belgium, and a second fellowship in genetics and teratology at Harvard University School of Medicine. Id. Dr. Raymond is board-certified in pediatrics, clinical genetics, and neurology, with special competency in child neurology. Id. He has had extensive clinical, instructional, and research experience in the fields of neurology, pediatrics, and genetics. See id. at 1-2, 9-10. He has peer reviewed and published numerous articles in these fields. See id. at 2-9. Dr. Raymond joined the University of Minnesota Medical Center in January 2013. Id. at 1. Since then, he has been working as a Professor and Physician of Pediatric Neurology in the Department of Neurology. Id.

3. Respondent's Expert, Dr. Rajesh Sachdeo

Dr. Rajesh Sachdeo is a neurologist who specializes in epilepsy. Resp.'s Ex. D at 1. He attended medical school at the Christian Medical College in Ludhiana, India. Id. After moving to the United States, Dr. Sachdeo completed his residency at Loyola University Medical Center in Maywood, Illinois. Id. He obtained his subspecialty training in epilepsy through a fellowship program at Rush-Presbyterian St. Luke's Medical Center in Chicago, Illinois. Id. at 2. Currently, Dr. Sachdeo is a Clinical Professor of Neurology at Rutgers University Robert Wood Johnson Medical School (formerly known as "University of Medicine and Dentistry of New Jersey") in New Brunswick, New Jersey. Resp's Ex. C at 1. He also serves as an attending physician at a number of hospitals, including the Robert Wood Johnson University Hospital, Princeton University Medical Center, and the Jersey Shore Medical Center. Id. He has been board-certified in neurology and neurophysiology since 1982. Id. Dr. Sachdeo has served on many committees and received a Humanitarian Award from the New Jersey Epilepsy Foundation. Id. He is active in clinical research and has conducted more than 50 studies on epilepsy. Id. Dr. Sachdeo has authored book chapters and more than 40 articles. Id. He is familiar with the standard of neurological care in the United States and has an active clinical practice of pediatric epilepsy. Id. Particularly, Dr. Sachdeo has seen and treated approximately 50 patients with Dravet syndrome. Id.

VI. Analysis

The undersigned evaluates petitioners' medical theory below. The undersigned has reviewed and considered all of the evidence in this case and the entire record as a whole. The following is by no means a complete recitation of all of the relevant facts and evidence considered. See §300aa-13(a) (stating that the special master should consider the "record as a whole").

A. Althen Prong One: Reliable Medical Theory

Under Althen Prong One, petitioners must set forth a medical theory explaining how the vaccines could have caused E.O.'s injury. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56. This prong requires petitioners to make an evidentiary showing that the vaccines E.O. received on April 9, 2009, "can" cause his alleged injury. Id. at 1356.

Petitioners' theory of causation need not to be medically or scientifically certain; however, it must be informed by a "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) (noting that the special master's decision is often "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) (holding that 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. Petitioner's First Proposed Mechanism: "Second Hit" Theory

Petitioners' expert, Dr. Shafrir, agrees that the SCN1A mutation is a necessary cause of Dravet syndrome, but he opines that the mutation alone is not sufficient to cause the disease. Pet'rs' Ex. 74 at 2. He proposes two alternative mechanisms whereby the vaccinations could have caused E.O.'s Dravet syndrome. Pet'rs' Ex. 68 at 5; Pet'rs' Ex. 102 at 8. The first proposed theory is that E.O.'s vaccinations may have been a "second hit." Pet'rs' Ex. 47 at 8. Dr. Shafrir cites Klassen et al.,[22] explaining that for many diseases, including cancer, it has "been hypothesized that the appearance and severity of the disorder are a simple result of the net accumulation of genetic variants or 'hits' in a disease pathway, where crossing an undefined risk threshold divides affected from unaffected individuals." Pet'rs' Ex. 47 at 3 (quoting Pet'rs' Ex. 48 at 1036). Dr. Shafrir further opines that "the occurrence of a single seizure, which here, was clearly induced by vaccination, make[s] the brain more prone to seizures from other causes." Id.

[22] Klassen, et al., 145 CELL 1036.

at 8. Dr. Shafrir concludes that a "single seizure can cause dramatic changes in gene expression in the brain, which may serve as the second hit mentioned by Klassen." Id.

Dr. Shafrir also described the "second hit" mechanism as a "gene-environment interaction." See Pet'rs' Ex. 28 at 16. He states that the abnormal gene is the "first hit," but he does not believe that the mutation alone would trigger Dravet syndrome without "an environmental effect (vaccination) that temporally shifts the age at onset." Id. at 16. Dr. Shafrir concedes that his second hit theory is "a new [and] very complex field of research," and studies in this particular area are still at "a very preliminary stage." Pet'rs' Ex. 47 at 8. Likewise, Dr. Shafrir acknowledges that studies to support this theory have not been performed in "Dravet syndrome or its animal mode[l]." Id.

Klassen, however, does not provide support for Dr. Shafrir's theory. In Klassen,[23] researchers performed exome sequencing of 237 ion channel subunit genes looking for exonic variations in 139 healthy controls and 142 persons with idiopathic epilepsy ("IE") and developed ion channel genomic profiles. In doing so, they found "remarkable genetic complexity and overlapping patterns of both rare and common variants in known excitability disease genes," in both the control and IE groups, "indicating that the potential for clinical expression of these common disorders is embedded in the fabric of all human genomes." Pet'rs' Ex. 48 at 1037.

Klassen used the phrases "two-hit" and "third-hit" to describe hypotheses derived from complex computational modeling of different genetic variations for the purpose of examining two different theories, the "load hypothesis" and the "single-cell" model. The load hypothesis suggests that "if IE is the result of accumulating mutations of small effect in known disease genes, then the "load" or summation of those deleterious mutations will surpass some liability threshold contributing to the overt excitability phenotype." Id. Pet'rs' Ex. 48 at 1038.

Klassen made three important findings, "[F]irst[,] that the architecture of ion channel variation …consists of dense and highly complex patterns of common and rare alleles; second, that structural variants in…epilepsy genes appear in otherwise healthy individuals; and third, that individuals with epilepsy typically carry more than one mutation in known [] epilepsy genes." Pet'rs' Ex. 48 at 1037. In conclusion, "[P]henotypic variation in epilepsy…may arise from a diverse array of channel alleles at a single focus, or a constellation of novel alleles in related or distant subunit genes." Id. So while Klassen suggests that mutations may combine to cause disease, the study did not examine vaccines or other environmental factors or draw conclusions about the theories proposed by Dr. Shafrir.

b. Petitioners' Second Proposed Mechanism: Immune-Mediated Response

[23] A full discussion of Klassen is far beyond the scope of this decision, but it appears that one of the goals of the research was to predict phenotypes using bioinformatics for the purpose of developing drugs to more effectively treat epilepsies. See Pet'rs' Ex. 48 at 1043.

Dr. Shafrir's second proposed mechanism is based on an immune-mediated response to the DTaP vaccination. One of his suggested immune responses is the mechanism of molecular mimicry. Pet'rs' Ex. 68 at 5; Pet'rs' Memo at 18. Dr. Shafrir opines that "components of the DTap vaccination contain multiple areas of homology with multiple brain proteins, including multiple ion channels in epilepsy related genes." Pet'rs' Ex. 102 at 5. Dr. Shafrir cites studies by Kanduc[24] in support of this theory. Kanduc's work, however, lacks persuasive authority because it dealt with potassium channel proteins, not sodium channel proteins, which are at issue here. See Pet'rs' Ex. 113. Moreover, when Kanduc studied the diphtheria toxin, he did not examine epilepsy-related genes. See Pet'rs' Ex. 102 at 6. Thus, Kanduc's findings do not support the existence of homology given the facts and circumstances of this case.

Dr. Shafrir also cites Obergon,[25] a study that deals with antibodies found in children with autism. According to Dr. Shafrir, in Obergon's study, autistic children were found to have antibodies to epitopes of the CASpr2 protein, which has been reported to have homology with part of the pertussis vaccine. See Pet'rs' Ex. 68 at 6. Petitioners hypothesize that children with SCN1A mutations have immune abnormalities that cause them to develop autoantibodies to the CASpr2 protein through the mechanism of molecular mimicry. Pet'rs' Memo at 20. According to petitioners' theory, CASpr2 is homologous to pertussis filamentous hemagglutinin, which is found in the TDaP vaccine. Id. at 20-21. Antibodies against CASpr2 may affect the potassium channel and cause an imbalance between excitation and inhibition in the brain's neuronal circuits, resulting in seizures. Id. at 21. Dr. Shafrir attempts to analogize the findings of the Obergon study to the facts here. But this case involves epilepsy and Dravet syndrome in children with an SCN1A mutation, and not autism, thus the analogy does not hold. Dr. Shafrir also recognized the limitations in the Obergon study when he stated, "It is important to remember that such a level of demonstration (referencing the Obergon study) of actual molecular mimicry with brain component [has] not been achieved with most immunizations." Pet'rs' Ex. 75 at 2.

Dr. Shafrir similarly opined that several different components of the DTaP vaccination are homologous with human proteins associated with epilepsy. Pet'rs' Ex. 102 at 5. He cites to studies, Lucchese et al.,[26] and Bavaro et al.,[27] to support this opinion. However, these studies

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[24] Kanduc, D., "Peptide Cross-Reactivity: the Original Sin of Vaccines," S4 FRONTIERS IN BIOSCIENCE 1393-401 (2012) [Pet'rs' Ex. 112]; see also Pet'rs' Ex. 113.

[25] Obergon, Demian, et al., "Potential Autoepitope Within the Extracellular Region of Contactin-Associated Protein-Like 2 in Mice," 4 BRITISH J. MED. & RESEARCH 416-432 [Pet'rs' Exs. 76, 116].

[26] Lucchese, Guglielmo, et al., "The Peptide Network Between Tetanus Toxin and Human Proteins Associated with Epilepsy," 2014 EPILEPSY RESEARCH AND TREATMENT 1-12 (2014) [Pet'rs' Ex. 113].

[27] Bavaro, Simona Lucia, et al., "Pentapeptide Sharing Between *Corynebacterium Diphtheria* Toxin and the Human Neural Protein Network," 33 IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY 360-72 (2011) [Pet'rs' Ex. 114].

were based on highly theoretical data, and the protein sequences were obtained from resources "built on information extracted from the studies on molecular biology of disease candidate genes with in-depth annotations of their function at the protein level derived from the current scientific literature." Pet'rs' Ex. 114 at 361. The authors of these two articles raise many interesting questions which require further study, but reach no conclusions as to whether the vaccines here share homology with epilepsy-related proteins.

In further support of their hypothesis, petitioners cite a study by Lilleker et al.[28]wherein researchers tested seizure patients for the presence of voltage-gated potassium channel complex antibodies ("VGKC Abs"), as well as other antibodies associated with epilepsy, and treated them with immunotherapy accordingly. Pet'rs' Ex. 77 at 776. The team reported that a patient with autoantibodies against CASpr2 stopped having seizures after undergoing immunosuppressive therapy. Id. at 777. Presumably, petitioners cite the Lilleker study to suggest that molecular mimicry occurred between the DTaP vaccine and CASpr2 because a patient with antibodies to CASPr2 responded to immunotherapy. This presumption, however, is overly simplistic, as Lilleker looked primarily at antibodies against the voltage-gated potassium channel complex, rather than the sodium channel, which is at issue here. Moreover, the researchers looked specifically at adult patients who had been newly diagnosed with unexplained epilepsy, and they did not make their results applicable to children with the condition or children with Dravet syndrome. Id. at 776.

Dr. Shafrir also relies on the works of Catarino[29] and McIntosh[30] for the position that Dravet syndrome is an immune mediated condition caused in part by vaccines. Pet'rs' Ex. 68 at 5. The authors of the McIntosh[31] study found that DTaP vaccination "triggered a significantly earlier onset of seizures," in patients with SCN1A mutations. See Pet'rs' Ex. 28 at 15. In the study, 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"). Id.; Pet'rs' Ex. 36 at 6. 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. Id. Based on the difference in onset, Dr. Shafrir opined that a vaccine "alters the course of seizures in children with SCN1A gene mutation." See Pet'rs' Ex. 28 at 14.

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[28] Lilleker, James, et al., "VGKC Complex Antibodies in Epilepsy: Diagnostic Yield and Therapeutic Implications," 22 SEIZURE 776-79 (2013) [Pet'rs' Ex. 77].

[29] Catarino, C.B., et al., "Dravet Syndrome as Epileptic Encephalopathy: Evidence From Long Term Course and Neuropathology," 134 BRAIN 2982-3010 (2011) [Pet'rs' Ex. 41].

[30] McIntosh, Anne M., et al, "Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study," 9 LANCET NEUROL. 592-98 (2010) [Pet'rs' Ex. 36].

[31] McIntosh et al., 9 LANCET NEUROL. 592.

Although he relied on the McIntosh study, Dr. Shafrir disagreed with its conclusion that there was "no difference between the two groups, vaccination-proximate and vaccination-distant," with regard to "intellectual disability," or "occurrence regression." Id. at 14-15. The McIntosh study, however, does not support Dr. Shafrir's theory because the results of the study show that children with Dravet syndrome experience regression and developmental delays regardless of whether they receive vaccinations.[32] Id. Similarly, the Catarino article does not support Dr. Shafrir's theory because the study found that 70 to 80 percent of adult patients with Dravet syndrome have an SCN1A mutation, and 90 percent of these mutations are de novo.[33]

Another article cited by Dr. Shafrir was authored by Black and Waxman,[34] who questioned whether those who have the SCN1A mutation have "some abnormalities in their immune function, in addition to abnormalities in the electrical activities in the brain." Pet'rs' Ex. 68 at 5. But Dr. Shafrir concedes that whether this "abnormality affects the response of the affected infants to the DTP or DTap vaccination is [] unknown." Id.

Respondent's expert, Dr. Raymond, disagreed with Dr. Shafrir's proposed theories and opined that the SCN1A mutation is the cause of E.O.'s Dravet syndrome. He explained that the SCN1A mutation affects neurons in the central nervous system. Resp's Ex. A at 6. Neuron cells maintain "an electrical potential or gradient" across cell membranes and deliver information signals with changes in the electrical potential. Id. The SCN1A gene "encodes a portion of a channel" that controls the flow and transport of sodium molecules across cell membranes in the neurons. Id. at 7. The sodium pores in the membranes serve as a "voltage responsive switch." Id. When the voltage meets a certain level, the pores allow passage of sodium ions from one side of the membranes to another. Id. The genetic abnormality that causes Dravet syndrome is a mutation of the "voltage-gated Na^+ channel subunit." Id. at 4. Thus, the mutation prevents the normal flow and transport of sodium molecules of neuron cells. SCN1A mutations have been associated with a variety of seizure disorders, including generalized epilepsy with GEFS+ and Dravet syndrome. Id. at 7. Specifically, "a relatively high percentage" of SCN1A mutations

[32] For a more detailed discussion of the McIntosh article, see infra p. 21. The undersigned also agrees with Snyder's similar reasoning regarding the McIntosh article. See Snyder, 2011 WL 3022544, at *23.

[33] For a more detailed discussion of the Catarino article see infra p. 25.

[34] Black, Joel A., & Waxman, Stephen G., "Sodium Channels and Microglial Function," 234 EXPERIMENTAL NEUROLOGY 302-15 (2012) [Pet'rs' Ex. 66].

have been found in patients diagnosed with Dravet syndrome. Id. at 4. Dr. Raymond cited works of Claes[35, 36] and Mulley[37] to support his opinion.

Claes et al. studied the DNA and SCN1A gene in seven patients with SMEI. Resp's Ex. A2 at 1327. The researchers found a heterozygous[38] mutation in the SCN1A gene of each of the seven patients which their parents did not have (de novo). Id. at 1329. Six of the seven patients had either a splice-site or nonsense mutation. Id. Claes et al. further observed that "in the majority of patients with SMEI, the mutation results in early termination of translation of the protein, thereby producing a C-truncated SCN1A protein ..." Id. at 1330. A later study by Claes et al. analyzed the mutations in the SCN1A gene of nine additional patients with Dravet syndrome. Resp's Ex. A7 at 615. As before, the researchers found that all mutations occurred de novo, with six missense, two nonsense, and one splice donor site mutation. Id. at 618. Similarly, Mulley et al. found that "the overwhelming majority of known mutations in SCN1A lead to severe myoclonic epilepsy of infancy…" Resp's Ex. A8 at 535. They further note that "[t]he percentage of SMEI patients carrying SCN1A mutations varies between 33 and 100 [percent]…. The majority of these mutations are novel changes." Id. at 537-38.

In essence, Dr. Raymond disagreed with Dr. Shafrir's proposed theories of second hit and immune-mediation/molecular memory, stating that the SCN1A mutation is the "sole cause" of E.O.'s Dravet syndrome. Id. at 1; see Resp's Ex. A at 13. The basis for Dr. Raymond's opinion is three-fold. First, the existing medical studies and literature have established that a significant alteration in the SCN1A gene alone is sufficient to cause Dravet syndrome. See Resp's Ex. E at 3-4. In contrast, Dr. Shafrir relied on studies that were not specific to SCN1A, or retrospective studies with methodology problems.[39] Id. Second, animal models have demonstrated significant abnormalities of SCN1A mutation that "mirror the human condition," and in these studies the animals spontaneously developed seizures without any triggers. Id. Third, the McIntosh et al.[40]

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[35] Claes, Lieve, et al., "De Novo Mutations in the Sodium-Channel Gene *SCN1A* Cause Severe Myoclonic Epilepsy of Infancy," 68 AM. J. HUM. GENET. 1327-32 (2001) [Resp's Ex. A2].

[36] Claes, Lieve, et al., "De Novo *SCN1A* Mutations Are a Major Cause of Severe Myoclonic Epilepsy of Infancy," 21 HUMAN MUTATION 615-21 (2003) [Resp's Ex. A7].

[37] Mulley, John C., et al., "*SCN1A* Mutations and Epilepsy," 25 HUMAN MUTATION 535-42 (2005) [Resp's Ex. A8].

[38] Heterozygosity is defined as "the state of possessing pairs of different alleles at one or more loci." Dorland's at 857.

[39] For example, some of the studies cited by Dr. Shafrir did not accurately document fever events for all the patients.

[40] Pet'rs' Ex. 36; see also Resp's Ex. A24.

and Berkovic et al.[41] studies show that the occurrence of febrile seizures following vaccinations does not change the clinical course or outcome of Dravet syndrome. See Resp's Ex. A at 11.

In the McIntosh et al. study, children with SCN1A mutations in the vaccination-proximate group had "the same genetic alternations" as those in the vaccination-distant group, and the clinical outcomes of the two groups were not significantly different. See Resp's Ex. E at 4; Resp's Ex. A at 12. Although the authors of the McIntosh[42] study found that DTaP vaccination triggered a significantly earlier onset of seizures in patients with SCN1A mutations, they concluded that children who had seizure onset within two days after vaccination, versus those that did not have seizures temporally associated with vaccine administration, experienced the same outcome of disability and regression. Pet'rs' Ex. 36 at 6.

Berkovic et al. had similar findings. In Berkovic, the authors performed a retrospective study of 14 patients who had a seizure within 72 hours of receiving the pertussis vaccination and who allegedly had vaccine encephalopathy. Pet'rs' Ex. 35 at 488. All 14 patients showed "severe epilepsy with multiple seizure types and intellectual disability," and eight of the 14 patients had SMEI. Id. at 489. Eleven patients had mutations in the SCN1A gene. Id. at 488. Berkovic cited four reasons why it was unlikely that the pertussis vaccination played a significant role in vaccine encephalopathy: first, although vaccinations can trigger seizures, "there is no evidence of long-term adverse outcomes[;]" second, more than half of the patients were afebrile when they had their first seizure, suggesting that fever is not essential; third, the neuroimaging data did not reveal evidence of "an inflammatory or destructive process[;]" and finally, missense mutations and truncation reported in "conserved parts of SCN1A" were not observed in hundreds of healthy controls. Id. at 491. Berkovic concludes that, "[I]ndividuals with [SCN1A] mutations seem to develop SMEI … whether or not they are immunized in the first year of life. We do not think that avoiding vaccination … would prevent onset of this devastating disorder in patients who already harbor the SCN1A mutation." Id.

Animal models have played an "extremely important" role in understanding the pathogenesis of Dravet syndrome. Resp's Ex. A at 7. One of these studies was described by Oakley.[43] Oakley's group studied mice that were created with an abnormal deletion of one copy of the SCN1A gene. Resp's Ex. A9 at 3. At birth, the mice appeared normal, but their conditions changed as they aged. Id. One group of mice was subject to hyperthermia, or increased temperature, until seizures were provoked. Id. The other group was not exposed to temperature elevations. Id. The latter group of mice subsequently developed seizures even though they were not exposed to elevated temperatures. Id. Young mice initially had only

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[41] Berkovic, Samuel, et al., "De Novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study," 5 LANCET NEUROL. 488-92 (2006) [Pet'rs' Ex. 35].

[42] McIntosh et al., 9 LANCET NEUROL. 592.

[43] Oakley, John C., "Temperature- and Age-Dependent Seizures in a Mouse Model of Severe Myoclonic Epilepsy in Infancy," 106 PNAS 3994-99 (2009) [Resp's Ex. A9].

febrile seizures, but as they aged, they spontaneously developed generalized and myoclonic seizures. Resp's Ex. A at 3-4. The mice developed seizure disorders without "any bacterial, viral, or immune altering agent or precipitant, including immunizations." Id. at 8. Thus, the animal studies show that there is no need to invoke environmental factors to explain seizure onset in the face of the SCN1A mutation. Id. at 9. Of particular interest to Dr. Raymond is the fact that the mice had conditions typically seen in Dravet syndrome in humans, including gait problems and behavioral abnormalities. Id. at 7. He concluded that the mouse model "recapitulates the human disease with surprising fidelity." Id. at 8.

c. Evaluation of the Evidence

Althen Prong One requires petitioners to set forth a reliable medical theory explaining how the vaccines E.O. received could have caused his alleged injury. Althen, 418 F.3d at 1278. While scientific certainty is not required to establish causation under the Act, the theory must be supported by a "sound and reliable" medical or scientific explanation. Id. at 1279; Knudsen, 35 F.3d at 548.

Here, the undersigned finds that petitioners have failed to provide preponderant evidence to support their medical theory. Dr. Shafrir did not provide a "sound and reliable" medical theory to explain how the vaccinations at issue cause Dravet syndrome. Although he proposed two theories of causation, second hit and immune-mediation, his opinions were not as persuasive as those of Dr. Raymond. In addition, none of the articles cited by Dr. Shafrir suggest that vaccines can cause Dravet syndrome or change the clinical course of Dravet syndrome, and several come to the opposite conclusion. While some studies demonstrate an association between vaccination and fever, and thus the onset of seizures in children with Dravet syndrome, the existing medical literature has established that vaccination does not affect the clinical course or prognosis of Dravet syndrome. The animal models, as presented by Dr. Raymond, provide strong evidence that Dravet syndrome will develop in children with the SCNIA mutation, whether or not they receive vaccinations.

B. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason" for E.O.'s injury. Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but-for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356. This requires petitioners to show that the vaccines E.O. received on April 9, 2009, actually caused the alleged injury. See Pafford, 451 F.3d at 1354. However, petitioners are not required to make a specific type of evidentiary showing. See Capizzano, 440 F.3d at 1325. 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." Id. Instead, petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Dr. Shafrir agrees that E.O. has the splice site mutation in his SCN1A gene and that E.O.'s clinical course is "very reminiscent of" Dravet syndrome. See Pet'rs' Ex. 28 at 11-12. However, Dr. Shafrir opined that E.O.'s risk of developing the syndrome was "dramatically increased" by his DTP vaccination. Id. at 12. He stated that the vaccines E.O. received on April 9, 2009, were a "significant factor" in causing his seizure disorder, encephalopathy, and subsequent injuries. Id. at 20. However, Dr. Shafrir concedes that even if E.O. had not received the vaccines, he could still have developed Dravet syndrome. Pet'rs Ex. 74 at 3.

Dr. Shafrir calculated the relative risks of the onset of Dravet syndrome following vaccination and attempted to generalize the theoretical statistics to E.O.'s specific case. Pet'rs' Ex. 28 at 13-16. His calculation was generated from the data provided in the Nieto-Barrera[44] article. Id. Dr. Shafrir reported that children who received the DPT vaccine had a 17.9 percent relative risk of experiencing their first seizure within 24 hours of vaccination. Id. at 13. Dr. Shafrir also noted that McIntosh reported an increased risk of seizure within 48 hours of the DTaP/DTP vaccine. Id. at 14 (referencing Pet'rs' Ex. 36). Dr. Shafrir highlighted McIntosh's discussion that vaccination may "trigge[r] the onset of Dravet syndrome, causing a temporal shift," but he attempted to refute the authors' main conclusion that vaccination does not affect the clinical course or outcome of Dravet syndrome, stating that the author misinterpreted the results due to the small sample size. Id. at 15-16 (referencing Pet'rs' Ex. 36).

Dr. Shafrir further disagreed that E.O.'s seizure onset was triggered by fever. See Pet'rs' Ex. 102 at 5. He explained that in the McIntosh study, only 33 percent of the vaccination-proximate patients had a fever at the onset of seizure.[45] Id.; Pet'rs' Ex. 28 at 14. He also cited the Zamponi et al.[46] study to eliminate the theory of fever mechanism. See Pet'rs' Ex. 54. Dr. Raymond opined that children with Dravet syndrome, including E.O., generally have their first seizure after febrile events.[47] Resp's Ex. E at 3. He cited the Nieto-Barrera[48] article to support this proposition. According to Nieto-Barrera, among children diagnosed with Dravet syndrome, the percentage of first seizure cases after any dose of DTP vaccination and the percentage of first seizure cases in conjunction with fever (not associated with vaccination) are equally high. Pet'rs' Ex. 34 at 620

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[44] See Nieto-Barrera, M., et al., "Severe Myoclonic Epilepsy in Infancy: An Analytical Epidemiological Study," 30 REV. NEUROL. 620-24 (2000) [Pet'rs' Ex. 34].

[45] In the McIntosh study, 12 out of 40 children had seizure onset either on the day of vaccination (n=5) or within 24 hours post-vaccination (n=7) and thus were defined as "vaccination-proximate" group. Only a third of the vaccination-proximate children (n=4) had a fever, defined as 100.4 degrees Fahrenheit or above. See Pet'rs' Ex. 36 at 594.

[46] Zamponi, Nelia, et al., "Vaccination and occurrence of seizures in SCN1A mutation-positive patients: a multicenter Italian study," 50 PEDIATRIC NEUROL. 228-32 (2014) [Pet'rs' Ex. 54].

[47] On the evening of his six-month vaccinations, E.O. presented to the ER of BJC Medical Center with a fever of 101.3 degrees Fahrenheit. Pet'rs' Ex. 1 at 13.

[48] Nieto-Barrera, M., et al., 30 REV. NEUROL. 620.

Dr. Raymond opined that E.O.'s Dravet syndrome was not caused or aggravated by any of the vaccines that he received on April 9, 2009. Resp's Ex. A at 13. E.O.'s SCN1A mutations are "splice site mutations," or more specifically, a deletion of four base pairs in the intronic region that cause unstable mRNA and lack of protein. Id. at 8. see also Pet'rs' Ex. 48.[49] Dr. Raymond explained that splicing defects like E.O.'s are a common cause of human genetic disorders and a cause of Dravet syndrome. Id. Dr. Shafrir agreed that "splice site mutations may be associated with absence of the entire nucleotide following exon in the final messenger RNA." Ex. 28 at 11. And essentially, Dr. Shafrir agreed with Dr. Raymond's interpretation of the genetic tests results that E.O.'s SCN1A mutation "affects an intron (non-coding area of a gene)," and probably plays a major role in his condition. Pet'rs' Ex. 74 at 4.

In his initial expert report, Dr. Shafrir stated that the only realistic way to determine whether E.O.'s specific mutation had an adverse effect was to find another patient with the same mutation, who had the same disease. Pet'rs' Ex. 28 at 11. Subsequently, E.O.'s mutation (IVS1+4_IVS1+7) was reported in another child who has Dravet syndrome. Resp's Ex. F2. In 2011, Zuberi et al.[50] published a retrospective analysis of genetic and clinical data in 273 persons with SCN1A mutations to determine how the "nature of a SCN1A mutation may influence the epilepsy phenotype." Resp's Ex. F2 at 594. Twenty four patients (nine percent) had splice site mutations, which is the type of mutation found in E.O. Id. at 595. In reviewing supplemental data provided by the authors, Dr. Raymond identified another person with E.O.'s mutation. Resp's Ex. F at 2. "[P]atient 11 had an intronic deletion of [four] base pairs."[51] Id. The mutation was subsequently added to an SCN1A database published by Meng et al.[52] The child with E.O.'s mutation was also described as having Dravet syndrome. Id.

Dr. Raymond further refuted Dr. Shafrir's opinion that the vaccinations caused E.O.'s Dravet syndrome by criticizing Dr. Shafrir's reliance on certain medical articles. See Resp's Ex.

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[49] Klassen et al. note, "Splice site mutations are implicated in channel disease due to dropout of exons from the coding messenger RNA (mRNA)." Pet'rs' Ex. 48 at 1038. The researchers describe these mutations as functionally severe. Id.

[50] See Zuberi, S.M., et al., "Genotype-Phenotype Associations in SCN1A-related Epilepsies," 76 NEUROLOGY 594-600 (2011) [Resp's Ex. F2].

[51] Zuberi reports the mutation as c.264+3del4 and list it in the SCN1A mutation database as IVS1+4_IVS1+7(2), which is the same mutation as E.O. Resp's Ex F at 2 (referencing Resp's Ex. F2). In reviewing the article's supplemental data, Dr. Raymond noted, "patient 11 had an intronic deletion of 4 base pairs. They report this as c.264+3del4. This was subsequently listed in a new SCN1A mutation database as IVS1+4_IVS1+7(2). The only information that the authors provide is that this child had classical Dravet syndrome (Dravet-C)." Resp's Ex. F at 2 (internal citations omitted).

[52] 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) [Resp's Ex. F1].

A at 10-13. Dr. Shafrir cited the Nieto-Barrera study to calculate relative risks for immunization and its relationship with seizure onset. Ex. 28 at 13-16 (citing Pet'rs' Ex. 34). Dr. Raymond noted that this article was published before genetic diagnostic methods of Dravet syndrome became available. Resp's Ex. A at 10. Without actual data of gene positive rates in that study cohort, any conclusions based on the study are flawed. Id. at 10.

Dr. Shafrir cited the works of Catarino[53] and Jozwiak[54] to support his opinions, but Dr. Raymond found the results of these two studies irrelevant and inapplicable to E.O.'s case. Resp's Ex. A at 12 (referencing Pet'rs' Exs. 41-42). Catarino et al. studied 22 adult patients with with Dravet syndrome, finding that 70 to 80 percent of Dravet syndrome cases occur due to SCN1A mutations, of which 90 percent occur de novo. Pet'rs' Ex. 41 at 2982-83. However, the goal of the study was to analyze Dravet syndrome in adult patients, in part to measure the long term course of the disease and determine "whether Dravet syndrome could [] be considered an epileptic encephalopathy later in life." Id. at 2984. As Dr. Raymond stated, "there is nothing in this report that demonstrates a role of environmental factors in the pathogenesis of Dravet syndrome." Resp's Ex. A at 12. The Jozwiak study, on the other hand, discussed seizure onset among infants with tuberous sclerosis, not Dravet syndrome. Pet'rs' Ex. 42. Dr. Raymond believed this study lacked "relevance to the disorders secondary to SCN1A mutations." Resp's Ex. A at 12.

Respondent's expert, Dr. Sachdeo, opined that E.O's clinical course and outcome are consistent with the expected course of Dravet syndrome. Resp's Ex. C. Based on E.O.'s medical records, Dr. Sachdeo described that E.O.'s seizures were resistant to any antiepileptic drugs and he exhibited symptoms of speech delay by 21 months. Id. at 4. E.O.'s vaccinations did not affect the natural clinical course or outcome of his Dravet syndrome. Id. at 5-6. He also clarified that while the SCN1A mutation might confer a "seizure susceptibility" to fever associated with vaccinations, the vaccinations did not trigger E.O.'s underlying genetic disorder. Id. at 5.

Dr. Sachdeo also noted the presence of primary generalized absence epilepsy on E.O.'s EEG results. Resp's Ex. C at 5. E.O.'s EEG results provided support for a genetic basis, as absence seizures[55] are "usually inherited with a susceptibility locus being described nearby the SCN1A gene." Id. Dr. Sachdeo cited the Consortium[56] article to support this proposition.

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[53] Catarino, et al., 134 BRAIN 2982.

[54] Jozwiak, Sergiusz, et al., "Antiepileptic Treatment Before the Onset of Seizures Reduces Epilepsy Severity and Risk of Mental Retardation in Infants with Tuberous Sclerosis Complex," XXX EUROPEAN J. PAEDIATRIC NEUROLOGY 1-8 (2011) [Pet'rs' Ex. 42].

[55] Absence seizures consist of "a sudden momentary break in consciousness of thought or activity, sometimes accompanied by automatisms or clonic movements, especially of the eyelids." Dorland's at 1688.

[56] EPICURE Consortium, et al., "Genome-Wide Association Analysis of Genetic Generalized Epilepsies Implicates Susceptibility Loci at 1q43, 2p16.1, 2q22.3 and 17q21.32," 21 HUM. MOL. GENET. 5359-72 (2012) [Resp's Ex. C6].

Consortium et al. conducted a genome-wide association study[57] on 3020 patients with genetic generalized epilepsies and a control group of 3954 epilepsy-free participants. Resp's Ex. C6 at 5361, 5367. This well-controlled study suggests that there is an association between generalized epilepsy syndrome and a loci nearby SCN1A gene. Resp's Ex. C6 at 5376. Based on this finding and the existing literature, Consortium et al. concluded that SCN1A mutation is a "genetic risk factor" for a wide spectrum of common epilepsy syndromes, including generalized epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome. Id.

Moreover, Dr. Sachdeo noted from E.O.'s medical records that his seizures did not respond adequately to medications and his speech delay became apparent by 21 months. Resp's Ex. C at 2-4. Dr. Sachdeo stated that E.O.'s drug resistance and developmental delay are consistent with the clinical course and outcome described by Charlotte Dravet,[58] the pediatric neurologist who first discovered this disease. Id. at 5. Dr. Sachdeo believed that E.O.'s condition was not affected by his vaccination, stating that "[E.O.'s] seizures would be drug resistant and his outcome [would] not change," even if he had not received vaccinations. Id. He cited the McIntosh study to support this opinion. Id. at 5 (citing Resp's Ex. A24). As stated earlier, in the McIntosh study, the seizure onset occurred 7.8 weeks earlier in the vaccination-proximate group; however, there were no other statistically significant differences between the two groups regarding subsequent seizure types, intellectual function, or prognosis. Id. at 5; Resp's Ex. A24 at 596.

Dr. Raymond explained why E.O.'s vaccinations did not cause his Dravet syndrome. He stated:

> Reviewing the clinical features in this case, [E.O.] is a child who at the age of [six] months had a brief febrile seizure without encephalopathy following his immunization. He subsequently developed multiple seizure types which were medically refractory. He continued to have sensitivity to elevations in temperature. [At approximately] two years of age, he manifested developmental issues including language delays and ataxia. His onset and course are consistent with his diagnosis of Dravet syndrome. Through genetic testing, he was determined to have a de novo alteration in the SCN1A gene that is predicted to result in alterations in splicing and therefore protein formation. This mutation has now been reported in another child with classical Dravet syndrome. Resp's Ex. F at 2.

a. Evaluation of the Evidence

[57] Genome-wide association studies have been considered as a "powerful and effective approach" to identify susceptibility genes in complex human diseases. See Resp's Ex C6 at 5361.

[58] Dravet, C., and Bureau, M., Severe myoclonic Epilepsy in Infancy (Dravet Syndrome). In Engle, J., Petdley, T., Epilepsy: A Comprehensive Textbook, 2nd Ed., Philadelphia: Lippincott Williams & Wilkins, pp. 2323-28 (2008) [Resp's Ex. C5].

Althen Prong Two requires preponderant evidence of a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in petitioners' case, the question is whether the vaccine (or vaccines) caused the alleged injury. Broekelschen, 618 F.3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case . . . ."); Pafford, 415 F.3d at 3.

Here, the undersigned finds petitioners failed to prove by a preponderance of the evidence a logical sequence of cause and effect showing that the vaccines E.O. received caused his Dravet syndrome. Although Dr. Shafrir relied on the McIntosh article to demonstrate his argument that the vaccinations may have triggered earlier seizures, he ignored the essence of the McIntosh study that neither vaccines nor time of seizure onset changes the clinical course or outcome in children with Dravet syndrome.

Moreover, as Dr. Raymond discussed in his expert report, Dr. Shafrir's attempts to demonstrate that vaccination causes Dravet syndrome are not persuasive. Dr. Shafrir's calculations of the relative risks for immunization were based on an article that lacked accurate data of gene positive rates, and he cited articles that were not relevant to E.O.'s situation.

In addition, E.O.'s medical records do not support evidence of cause and effect. Although E.O.'s treating physicians and EMS caregivers reported that his initial seizure was temporally associated with vaccinations, none of them attributed his development of Dravet syndrome to the vaccines. Rather, Dr. James Wheless, E.O.'s pediatric neurologist, first diagnosed him with complex partial seizures "secondary to SCN1A gene defect" at the age of 21 months. Pet'rs' Ex. 18 at 26.

Further, the splice site mutation identified in E.O.'s SCN1A gene, as explained by Dr. Raymond, is associated with the dysfunction of the voltage-gated sodium channel, and causally associated with Dravet syndrome. Resp's Ex. A at 3, 8. Dr. Raymond explained that splicing defects are common causes of genetic diseases, including Dravet syndrome. A child with the same SCN1A mutation as E.O. who also has Dravet syndrome has been reported in a SCN1A database. The finding of the same mutation in a child with the same illness is very persuasive evidence that the SCN1A mutation is the cause of E.O.'s Dravet syndrome.

C. Althen Prong Three: Proximate Temporal Relationship

Under Althen Prong Three, petitioners must establish that E.O.'s injury occurred within a time frame that is medically acceptable for the alleged mechanism of harm. See Pafford, 451 F.3d at 1358 (noting that evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury and the vaccination under the 'but-for' prong of the causation analysis). Petitioners may satisfy this prong by producing preponderant proof that the onset of E.O.'s seizures "occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." See de Bazan v. Sec'y of Health & Human Servs., 539 F.3d, 1347, 1352 (Fed. Cir. 2008); see also Faoro, 2016 WL 675491, at *31.

Petitioners may meet their burden by showing: (1) when the injury for which they seek compensation first appeared after vaccination; and (2) whether the period of symptom onset is "medically acceptable to infer causation." See 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 F. App'x 953 (2013) (per curiam); see also Faoro, 2016 WL 675491, at *31. The acceptable temporal association will vary according to the particular medical theory advanced in the case. Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting vaccine and injury"), aff'd sub nom. Veryzer v. United States, 475 F. App'x 765 (Fed. Cir. 2012); see also Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) (holding "a proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury").

All of the experts agree that E.O. had his initial seizure on April 9, 2009, the same day he received vaccines, but they disagree as to the significance of this fact. Dr. Shafrir opined that the DPT vaccine given to a child with Dravet syndrome creates a "12-fold higher risk" of the child having seizures within 48 hours, indicating a "tight medically appropriate temporal association between the vaccination and the onset of seizures," in those with the SCN1A mutation. Pet'rs' Ex. 47 at 9. Dr. Shafrir also opined that the vaccines triggered the onset of E.O.'s Dravet syndrome and the "initial presentation of [E.O.'s] epileptic encephalopathy."[59] Id.; Pet'rs' Ex. 28 at 11.

Dr. Raymond disagreed with Dr. Shafrir's conclusion that E.O.'s first seizure on April 9, 2009, marked the onset of his encephalopathy. Resp's Ex. A at 9. After his initial seizure on April 9, 2009, E.O. recovered and returned to baseline, and he did not show evidence of any injury that was temporally associated with the vaccines. Id. E.O.'s encephalopathy did not manifest until later, at approximately 21 months of age, which "is consistent with the temporal profile of [Dravet syndrome] and not to an adverse event subsequent to a brief seizure following immunization." Id.

Dr. Raymond also disagreed that the temporal relationship between the vaccines and the first seizure should be explained as "precipitating the disease." See Resp's Ex. A at 10. Although E.O. had "brief febrile seizure[s]," within 24 hours of his six-month immunizations, after his initial seizure, he returned to baseline and did not experience further seizures for over two months.

a. Evaluation of the Evidence

[59] Dr. Shafrir concedes that E.O.'s initial presentation of illness did not meet the definition of encephalopathy as defined by the Vaccine Act. See Pet'rs' Ex. 28 at 12.

The medical records show, and all of the experts agree, that E.O's initial seizure, or seizure onset, was within 24 hours of his six-month vaccinations. While the proximity between vaccination and seizure onset might suggest a causal relationship between the two events, E.O. did not develop Dravet syndrome until approximately 21 months of age, more than a year after these vaccinations. Without evidence of a causal mechanism or evidence of injury, the temporal relationship between the vaccination and the first seizure alone is not sufficient to establish a causal link. See Veryzer, 100 Fed. Cl. at 356; see also Grant, 956 F.2d at 1148. Thus, the undersigned finds that petitioners have failed to meet their preponderant burden under Althen Prong Three.

D. Standards for Adjudication - Significant Aggravation

The second issue presented by the parties is whether E.O.'s vaccinations significantly aggravated his pre-existing injury. Pet'rs' Memo at ¶ 56. 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 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.

E. Significant Aggravation Theory

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

The first step in the Loving test is to determine E.O.'s condition before he received the vaccinations at issue. E.O. was born with a mutation of his SCN1A gene. Loving, 86 Fed. Cl. at 144. The specific mutation here is a "splice site" mutation that affects the function of the protein. Resp's Ex. A at 8. Mutations of this type are associated with Dravet syndrome. Id. Although E.O. was born with the SCN1A mutation, his physical and neurological examinations were all normal prior to his April 9, 2009 vaccinations. Pet'rs' Ex. 28 at 11. He was healthy and did not have any seizures prior to the vaccinations.

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

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

After the initial febrile seizure on April 9, 2009, E.O. returned to baseline, did not exhibit symptoms of encephalopathy, and he did not have any other seizures until June 16, 2009. Pet'rs' Ex. 19 at 190-92. Upon admission to the hospital on June 16, 2009, he was afebrile, awake, alert, and no distress was noted. Id. at 191. On June 18, 2009, E.O. saw Dr. Sekul at MCG, who noted that his development was normal. Pet'rs' Ex. 4 at 85. On August 17, 2009, E.O.'s CT scan, EEG, repeat EEG, and brain MRI were all normal. Pet'rs' Ex. 2 at 5-6. On September 16, 2009, at 11 months old, his development was still considered normal. See Pet'rs' Ex. 19 at 168.

Over the next six months, E.O. began to experience prolonged seizures, and on March 1, 2010, he was admitted to the ICU at MCG. Pet'rs' Ex. 4 at 54-70. Although he was prescribed a variety of medications, his seizures could not be controlled. Pet'rs' Ex. 9 at 7, 32. On June 1, 2010, E.O. tested positive for the SCN1A mutation. Id. at 36-37. After he was placed on a ketogenic diet, some improvement was noted. Id. at 37-38. E.O.'s developmental delay became apparent at 21 months. Pet'rs' Ex. 18 at 26; Resp's Ex. C at 4. On July 19, 2010, Dr. Wheless performed a neurologic exam on E.O. and diagnosed him with "encephalopathy characterized by speech delay." Pet'rs' Ex. 18 at 25-26.

In summary, E.O. was "completely normal prior to the onset of the seizures and continued to be normal through the second year of life …. His initial EEG was normal. His MRIs were normal..." Ex. 28 at 11. He progressively developed multiple types of seizures, and atypical absences seizures. Id. "Similar to other patients with Dravet syndrome, he is very sensitive to fever." Id. The evidence in the record indicates and all of the experts agree that E.O.'s current condition is consistent with that of a child who has the SCN1A gene mutation and Dravet syndrome. Ex. 28 at 11.

(3) Loving Prong 3: Does E.O.'s Current Condition (or Condition After Vaccination) Constitute a "Significant Aggravation" of his Condition Prior to Vaccination?

The next prong of the Loving test is to determine whether there is a "significant aggravation" of E.O.'s condition by comparing his condition before vaccination to his 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 above, E.O. had a seizure after his April 9, 2009 vaccinations but returned to baseline condition after that seizure. Subsequently, as Dr. Shafrir notes, E.O. "showed dramatic recovery even after prolonged seizures," and after having a seizure at age ten months was described as laughing, smiling, and very active. Pet'rs' Ex. 28 at 10. Dr. Shafrir continues, "[v]ery unfortunately, towards the end of the second year of [his] life, there seemed to be a progressive slowing in [E.O.'s] development." Id. "On formal testing, at 21 months, his receptive language was

normal, but his expressive language was significantly delayed." Id. Over time, E.O.'s condition deteriorated and he developed severe epilepsy and developmental delay.

The undersigned must first make clear that there is no question that E.O.'s condition after his April 9, 2009 vaccinations changed and over time became worse. However, the question relevant to this factor of the Loving analysis is whether E.O.'s vaccination significantly aggravated his Dravet syndrome. In other words, is E.O.'s clinical course and outcome any different than it would have been if he had not been vaccinated? See Locane v. Sec'y of Health & Human Servs., No. 99-599V, 2011 WL 3855486, *10-11 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), aff'd, 99 Fed. Cl. 715 (Fed. Cl. 2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012) (affirming the special master's finding that petitioner's condition was not inconsistent with the disease generally and not affected by the vaccinations).

Dr. Shafrir suggests that if E.O. had not received the vaccines on April 9, 2009, the onset of his Dravet syndrome would have been later, his developmental delay may have been less severe, or that he may not have developed an illness at all. Pet'rs' Ex. 28 at 14; Pet'rs' Ex. 47 at 5, 8; Pet'rs' Ex. 74 at 3. All of these arguments fail, however, because Dr. Shafrir concedes that there is no way to predict what E.O.'s outcome would have been if he had not received the vaccines. Pet'rs' Ex. 74 at 3; Pet'rs' Ex. 102 at 4. And Dr. Shafrir concedes that E.O.'s clinical course is "very reminiscent of" Dravet syndrome. Pet. Ex. 28 at 13. Simply stating what "may" have happened is a matter of speculation and does not provide petitioners with preponderant evidence to support their theory.

Moreover, Dr. Shafrir's opinion that earlier onset of seizures changes the clinical course of children with Dravet syndrome contradicts the conclusion of the McIntosh study, which 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. Pet'rs' Ex. 36 at 6.

Petitioners have failed to show by a preponderance of the evidence that the vaccinations significantly aggravated E.O.'s condition. He was born with the SCN1A mutation and his clinical course developed consistently with that condition. The undersigned finds that the vaccinations did not change his clinical course and thus did not significantly aggravate his preexisting condition. See Snyder v. Sec'y of Health & Human Servs., 553 F. App'x. 994 (Fed. Cir. 2014) (holding 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 above, petitioners failed to establish by preponderant evidence a medical theory causally connecting E.O.'s condition, or any significant aggravation. Therefore, petitioners also fail to prove a theory as to significant aggravation.

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

For the same reasons set forth in section VI above, petitioners failed to prove by preponderant evidence a logical sequence of cause and effect showing that the vaccination significantly aggravated E.O.'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 Prong III of Althen. 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 VI(C), petitioners failed to preponderantly prove Prong Three of Althen, which is the last element of the Loving test.

F. Alternative Causation

Because petitioners did not meet their burden of proof on causation or significant aggravation, respondent does not have the burden of establishing that a factor unrelated to the vaccination caused E.O.'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 E.O.'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 E.O.'s Dravet syndrome and resultant neurological injuries. Compensation has been denied in a number of similar cases[60] 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).

[60] See infra note 3 for list of SCN1A cases in which compensation was denied.

In the Deribeaux case, the infant, M.D., received the DTaP vaccine at about six months of age. Deribeaux, 717 F.3d at 1364. The next day, M.D. had a prolonged seizure, and she was ultimately diagnosed with a seizure disorder. Id. Her parents filed a case in the Vaccine Program alleging that the DTaP vaccine triggered M.D.'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"). M.D. subsequently underwent genetic testing which revealed that she had an 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 M.D.'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 introduced evidence that the vaccine caused a fever, triggering M.D.'s initial seizure, but that the cause of the seizure disorder and resulting neurological injuries were 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 and found that the SCN1A mutation was the "sole substantial factor" in causing M.D.'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. 36 2012), cert denied, 133 S. Ct. 2022 (Apr. 29, 2013), affirmed the special master's finding that the SCN1A gene mutation, not the DTaP vaccine, caused only a "single, isolated initial febrile seizure," and was thus solely responsible for the vaccinee's SMEI. 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 F. App'x. 994, 999 (Fed. Cir. 2014), that the "Secretary proved by preponderant evidence of its 'factors unrelated' defense by showing that the gene mutations were the sole cause of the disorders." Id. at 999.

Three SCN1A cases were recently on review at the Court of Federal Claims. In all of the cases, the Court upheld the special masters' denial of 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. Id. at 110.

In Barclay, the Court upheld the special master's determination that the vaccine did not aggravate or worsen the child's genetic condition. Barclay v. Sec'y of Health & Human Servs.,

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. 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 E.O.'s SCN1A mutation, a factor unrelated to the administration of the vaccines, is the agent solely responsible causing his Dravet syndrome.

a. Althen Prong One: Respondent's Medical Theory

To prove Althen Prong One establishing alternative causation, respondent is required to set forth a medical theory explaining how a factor unrelated to the vaccine caused the injury at issue.

Respondent's expert, Dr. Raymond, explained the mechanism underlying Dravet Syndrome, stating:

> 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's Ex. A at 7 (internal citations omitted).

The medical articles and studies filed in this case 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[61] study, reporting on a five year study of data collected in the United Kingdom on patients with Dravet syndrome, describe the mutation as the "primary genetic cause" of the disease. Pet'rs' Ex. 55 at 2329. 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. at 2334.

Likewise, Professor Dr. Berten Ceulemans from the Department of Child Neurology at the University of Antwerp, Belgium, and her colleagues conducted a clinical study[62] on 60 patients with Dravet syndrome. Dr. Ceulemans concluded that there "is a strong argument

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[61] Brunklaus, A., et al., "Prognostic, Clinical, and Demographic Features in SCN1A Mutation-Positive Dravet Syndrome," 135 BRAIN 2329-36 (2012) [Pet'rs' Ex. 55].

[62] Claes, Lieve, et al., "De Novo SCN1A Mutations Are a Major Cause of Severe Myoclonic Epilepsy of Infancy," 21 HUMAN MUTATION 615-21 (2003) [Resp's Ex. A7].

favoring the genetic disorder itself as probably being the most important factor for developmental problems in these [Dravet syndrome] patients." Resp's Ex. A7 at 4. In the McIntosh study, the authors corrected their previous misunderstanding as to "presumed vaccine encephalopathy" as follows:

> We previously reported a retrospective analysis in which 12 of 14 patients with presumed vaccine encephalopathy in fact had previously unrecognized Dravet syndrome, 11 of whom had mutations in SCN1A. This showed that vaccination was wrongly blamed as an acquired cause of a genetic disorder, and the hypothesis that vaccination was the causal factor in our cohort could be rejected. Pet'rs' Ex. 36 at 596.

Dr. Raymond also explained that Dr. Shafrir held an oversimplified view of splice site mutations. Resp's Ex. A at 9. Dr. Raymond stated that the splice mutation in E.O.'s gene is associated with the dysfunction of the voltage-gated sodium channel, which is causally associated with Dravet syndrome. Id. at 8. This type of deletion results in unstable mRNA and no protein production and thus causes disease. Id. Therefore, the undersigned finds by a preponderance of the evidence that respondent has satisfied Althen Prong One.

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 E.O.'s Dravet syndrome and neurological injury. E.O. developed Dravet syndrome as a result of his genetic mutation, not because he received vaccinations. According to Dr. Raymond, even assuming that E.O. had an earlier onset of his seizure disorder, this would not alter his clinical course or outcome. Resp's Ex. E at 4. As explained by Dr. Sachdeo, "There is no evidence that … [E.O.] would not have developed Dravet syndrome regardless of having received [a] vaccination." Resp's Ex. C at 5. Dr. Raymond and Dr. Sachdeo rely on the McIntosh and Brunklaus articles, respectively, in support of their propositions. Dr. Raymond also testified that E.O.'s SCN1A mutation is the "sole cause" of his seizure disorder, developmental delay, and all of the other features of Dravet syndrome. Resp's Ex. A at 8, 13. Both Dr. Raymond and Dr. Sachdeo opine that it is not necessary to invoke an environmental factor, like the vaccination, to explain E.O.'s condition. Id.; Resp's Ex. C at 6. The undersigned thus finds by a preponderance of the evidence that respondent has satisfied Althen Prong Two.

c. Althen Prong Three: Timing

The last element of causation is proof of a proximate temporal relationship between the gene mutation and the injury. Althen, 418 F. 3d at 1278. E.O.'s alleged injury is his Dravet syndrome and his resulting neurological complications. 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 E.O.'s initial seizure. E.O. did not manifest the criteria for Dravet syndrome until he was over 21 months old, and thus there is no temporal relationship between his vaccinations and the onset of his Dravet syndrome. Moreover, E.O. had no encephalopathy after the vaccinations at issue. Therefore, E.O. did not have an injury that was temporally associated with the vaccines on April 9, 2009. His initial seizure was, in

hindsight, a suspicious sign that he might develop Dravet syndrome, or the initial manifestation of his genetic mutation. That fact alone does not establish a vaccine-related injury. Respondent's experts, on the other hand, state that E.O.'s clinical course, timing of the onset of his initial seizure, and overall outcome were consistent with Dravet syndrome. Therefore, the undersigned finds by a preponderance of the evidence that respondent has satisfied Althen Prong Three.

VII. Conclusion

For the reasons discussed above, the undersigned finds that petitioners have not established entitlement to compensation and that their petition must therefore be dismissed.[63] In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, the Clerk of Court SHALL ENTER JUDGMENT consistent with this decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master

[63] As discussed in note 3 above, there have been at least 15 other Program cases involving alleged vaccine injuries which were found to be attributable to SCN1A mutations. In the absence of further medical and/or scientific developments in such cases, the undersigned is unlikely to be persuaded of vaccine causation. Likewise, the undersigned will be disinclined to find a reasonable basis to compensate the attorneys and/or experts involved in such cases.