In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 06-868V
Filed: September 26, 2012
To be Published

CLAIRE BARNETTE, a minor, by her mother, KAREN BARNETTE and father, TIMOTHY BARNETTE	*	
Petitioners,	*	Entitlement denied; Severe Myoclonic Epilepsy of Infancy (SMEI); Dravet Syndrome; SCN1A Gene Mutation; Significant Aggravation
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Michael J. McLaren, Black and McLaren, Memphis, TN, for Petitioners.
Ann Donohue Martin, U.S. Department of Justice, Washington, D.C., for Respondent.

DECISION[1]

GOLKIEWICZ, Special Master.

Petitioners, Karen and Timothy Barnette, seek compensation on behalf their daughter, Claire Barnette ("Claire"), who suffers from Dravet Syndrome, which is also known as Severe Myoclonic Epilepsy of Infancy ("SMEI").[2] Petitioners allege that vaccinations Claire received

[1] The undersigned intends to post this decision on the website for the United States Court of Federal Claims, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). **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). Otherwise, the entire decision will be available to the public. Id. Any motion for redaction must be filed by no later than fourteen (14) days after filing date of this filing. Further, consistent with the statutory requirement, a motion for redaction must include a proposed redacted decision, order, ruling, etc.**

[2] Dravet Syndrome (also known as severe myoclonic epilepsy of infancy; SMEI) is characterised by onset of seizures around 6 months of age. Initial seizures are usually prolonged convulsions, either generalized or hemiclonic, often triggered by fever. Other seizure types that subsequently develop include myoclonic, partial, absence, and atonic

on September 19, 2005, significantly aggravated "her condition because they led to an earlier onset which resulted in a worse outcome." Petitioner's Post Hearing Reply Brief (P Reply) at 5. Respondent denies that Claire's vaccinations significantly aggravated her condition. Respondent alleges that Claire's condition is caused solely by a genetic mutation in her SCN1A gene. The undersigned finds that petitioners have failed to establish by a preponderance of the evidence that Claire's vaccination caused or significantly aggravated her condition.

I. INTRODUCTION and PROCEDURAL BACKGROUND

Petitioners filed on December 21, 2006, a Petition ("Pet.") pursuant to the National Childhood Vaccine Injury Act of 1986, as amended, 42 U.S.C. §§ 300aa-10 et seq. (2006)[3] ("Act" or "Program"). The Petition seeks compensation for injuries allegedly sustained by petitioners' minor child, Claire Barnette, from a Pediarix[4] immunization administered on September 19, 2005. Pet. at 1.

Significant development of the case followed the filing of the Petition. In summary, petitioners obtained and filed the majority of the required medical records with the Petition on December 21, 2006. See Petitioners' Exhibits ("P Exs.") 1-25. To support their Petition, petitioners filed on June 8, 2007, the expert report of Dr. James Wheless. P Ex. 26. The undersigned conducted a status conference on June 29, 2007, and informed the parties that petitioners' expert report was lacking a sufficient explanation of his theory of vaccine causation in this case. See Minute Entry filed June 29, 2007. Thereafter, petitioners sought and were awarded numerous enlargements of time over a period of almost two years to file a supplemental expert report from Dr. Wheless. See Orders filed July 2, 2007, August 6, 2007, October 15, 2007, December 17, 2007, January 17, 2008, March 5, 2008, May 5, 2008, July 3, 2008, August 25, 2008, and October 31, 2008. On May 18, 2009, petitioners filed an expert report from Dr.

> seizures. From the second year of life, intellectual development in these infants begins to plateau or regress, resulting in intellectual disability. About 70-80% of children with Dravet Syndrome have mutations in SCN1A, of which 95% are de novo.

P Ex. 92, R Ex. MM, McIntosh et al., Effects of Vaccination on Onset and Outcome of Dravet Syndrome: a Retrospective Study, 9 Lancet Neurol. 592 (2010). The terms Dravet, Dravet Syndrome and SMEI are used synonymously throughout this Decision.

[3] This Program comprises 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 et seq. (2006) (hereinafter "Program," "Vaccine Act," or "the Act"). Hereafter, individual section references will be to 42 U.S.C. §§ 300aa of the Act.

[4] The undersigned notes that while petitioners largely implicate the acellular pertussis component of the Pediarix vaccination Claire received on September 19, 2005 the undersigned considered whether there was any reliable evidence that any of Claire's September 19, 2005 vaccinations significantly aggravated her condition. Pediarix "is a combination product containing DTaP, hepatitis B, and inactivated polio vaccines." See Pediarix Vaccine: Questions and Answers at http://www.cdc.gov/vaccines/vpd-vac/combo-vaccines/pediarix/faqs-hcp-pediarix.htm (last visited September 18, 2012).

Eric Gershwin instead. See P Ex. 32. Respondent filed on October 15, 2009, her Rule 4(c) Report, recommending against compensating this Petition. Respondent's 4(c) Report was supported by the expert reports of Dr. J. Lindsay Whitton, Respondent's Exhibit (R Ex.) A, and Dr. Harley Morgan. R Ex. K.

Dr. Morgan's report addressed for the first time a laboratory report filed by petitioners on November 18, 2008, P Ex. 26 at 246-256, of an SCN1A DNA Sequencing Test performed on Claire that indicated Claire possesses a mutation in the SCN1A gene. R Ex. K at 3-6. At that time the variant was of unknown significance, P Ex. 29 at 246; however, Dr. Morgan opined it was "convincing for alternative cause for [Claire's] epilepsy" and that "[a] role for the demonstrated mutation in [Claire's] SCN1A mutation should be thoroughly investigated." R Ex. K at 6. With the implications of the SCN1A gene mutation, the case necessarily re-focused to address this significant issue.

Thereafter, petitioners sought and were granted additional time to file supplemental expert reports from Drs. Gershwin and Wheless. See Orders filed November 13, 2009, December 17, 2009, March 24, 2010, May 10, 2010, and July 20, 2010. Petitioners filed a supplemental expert report from Dr. Gershwin on April 13, 2010. P Ex. 55. Petitioners filed Claire's Revised SCN1A DNA Sequencing Test reports on July 14, 2010. P Exs. 87-88. Petitioners filed supplemental expert reports from Dr. Wheless on August 11, 2010, and October 29, 2010, P Exs. 90, 94, and a supplemental expert report from Dr. Gershwin on March 4, 2011. P Ex. 103.

Thereafter, petitioners filed an expert report from clinical geneticist, Dr. Fran Kendall, and further supplemental reports from Drs. Wheless and Gershwin. See P Ex. 111; P Ex. 116; P Ex. 117. Respondent filed responsive expert reports on June 3, 2011, from clinical geneticist Dr. Gerald Raymond, and clinical neurologist Dr. Max Wiznitzer. R Ex. P; R Ex. R.

An evidentiary Hearing was conducted on January 19 and 20, 2012, to elicit testimony from the parties' experts. Petitioners decided to rely upon the testimony of Drs. Kendall and Wheless. Respondent elected to rely on the testimony of Drs. Raymond and Wiznitzer. Thereafter, the parties filed their Post-Hearing Briefs. The record is complete and the case is ripe for decision.

II. FACTUAL HISTORY

The undersigned notes that the parties do not dispute the factual history in this case. The medical records are extensive. Only the pertinent medical records and information are summarized below.

Claire was born on March 18, 2005. P Ex. 2 at 1. On May 23, 2005, and July 19, 2005, Claire received the following vaccinations, with no recorded adverse consequences: Pediarix, Hib, and Prevnar. P Ex. 3; P Ex. 4 at 8, 13.[5] At six months of age, Claire received a third set of

[5] Claire's vaccination records indicate her second set of immunizations were administered on July 19, 2005. P Ex. 3. However, the medical records of Dr. Michael Lacy indicate this set of immunizations was administered on July 18, 2005. P Ex. 4 at 13-16.

Pediarix, Hib, and Prevnar vaccinations on September 19, 2005. P Ex. 3; P Ex. 4 at 19. That evening Claire suffered her first seizure. Petitioners contacted emergency services who responded, examined Claire, and declared her to be "okay." P Ex. 24 at 2; P Ex. 25 at 2. Claire was not taken to the hospital; rather she was taken to the pediatrician the following day for examination. P Ex. 4 at 21. The pediatrician's records indicate a "chief complaint" of

> ?seizure with the onset of 9/19/05. Location was given as left arm rhythmic jerking. The duration of symptoms was 1 Minute. Modifying factors were s/p vaccines yesterday. Associated signs/symptoms were head turned rightward, less responsive ~ 1 minute. Pertinent negatives given as no fever, no loss of consciousness.

P Ex. 4 at 21. Claire was found by the pediatrician's office to be "alert," "active," in "no distress," and "oriented." Id. at 22. Upon neurological exam Claire was found to have "good strength and tone, equal movements, [and] no focal findings." Id. It was noted Claire had an "[a]pparent seizure post vaccinations," and a plan was made for a neurology consult and an EEG. Id. at 23.

On October 4, 2005, Claire was taken to the emergency unit at North Oak Regional Medical Center for "seizure activity." P Ex. 5 at 1. She had a "runny nose" at that time and was receiving "Dimetap" to treat it. Id. at 4. Claire was noted to be in "no acute distress" and "smil[ing]." Id. at 2. The "clinical impression" by the emergency room doctor was "[diagnosis] seizure disorder" and Claire was transferred to Le Bonheur Children's Medical Center where she was admitted and diagnosed with a "focal seizure." Id.; P Ex. 6 at 1-2. Claire was treated with Trileptal, instructed to follow-up with neurologist, and to obtain an outpatient MRI and EEG prior to the appointment with the neurologist. P Ex. 6 at 2. Claire was discharged on October 5 with a notation that she suffered an "Injury and Illness" of "Seizure: New Onset (unk[nown] cause)." Id. at 6.

Claire saw neurologist, Dave Clark, at LeBonheur Children's Medical Center on October 12, 2005. Dr. Clark indicated Claire presented with a complaint of "[t]wo partial seizures, the last of which occurred approximately 1 week ago." P Ex. 7 at 1. Dr. Clark noted that Claire's first seizure was "immediately after her six-month vaccinations, however she had both her two and four month shots without any noted seizures." Id. Dr. Clark noted Claire's CT scan was normal, but "an EEG revealed scattered C4, F4 sharp and spike wave discharges. There were also infrequent discharges in the left frontal head region." Id. at 2. Claire was found by Dr. Clarke to be "[d]evelopmentally, age appropriate" and "playful" upon examination. Id. Dr. Clarke requested that an MRI be preformed, to continue the seizure "mode of management," and to schedule a follow-up appointment in a month or two. Id. No causative factor for Claire's seizures was indicated. Id.

Claire had another seizure on October 16, 2005. P Ex. 9 at 2. She was diagnosed with a seizure disorder and her Trileptal dosage was increased. P Ex. 9 at 3, 5. An MRI was conducted on October 19, 2005, and was found to be normal, with the exception of "inflammatory changes" to her right sinus. P. Ex. 29 at 3. A later MRI completed on March 13, 2006, after Claire was

admitted to the hospital again for seizures, was also found to be a "[n]ormal study with interval resolution of sinus disease seen on previous exam." Id. at 4.

Thereafter, Claire continued to experience seizures and was followed by Dr. Clarke for what emerged as intractable, multi-focal epilepsy, which proved resistant to drug therapy. See P Ex. 29 at 10, 13, 107, 176, 183. On June 24, 2008, at the age of 39 months, Claire was placed on a vagal nerve stimulator to treat her refractory epilepsy. P Ex. 29 at 263-64, 270-271. At that time, the medical records indicate Claire was developmentally delayed and in speech therapy. Id. at 263-64.

On June 11, 2008, a whole blood sample was taken from Claire and provided to Athena Diagnostics laboratory for a SCN1A DNA Sequencing Test. P Ex. 88 at 1. The test results revealed for the first time that Claire has a "DNA sequence variant or combination of variants ..." Id. At that time the significance of Claire's SCN1A variant was unknown and testing of her parents was "strongly recommended." Id. Additional, testing was conducted and a revised report was produced by Athena Diagnostics indicating Claire's parents do not have the same mutation, demonstrating Claire's mutation arose de novo. Id. Finally, a second revised report was produced by Athena Diagnostics in July of 2010, which indicated that Claire's genetic mutation, previously of unknown significance, was "re-classified as a known disease-associated mutation." Id. The report further indicated that as Claire's mutation arose de novo it "further increases the probability that this known disease associated mutation could be causative of a severe phenotype." Id. The laboratory report found that Claire's "test result is consistent with a diagnosis of, or a predisposition to developing, the severe phenotypes associated with SCN1A mutations, SMEI or SMEB." Id.

Claire is currently under the care of Dr. Wheless. Dr. Wheless' most recently filed records from November 7, 2011, indicate that Claire suffers an "[i]ntractable, symptomatic partial seizures with secondary generalization of independent hemisphere origin and atypical absence seizure[s] both under good control (secondary to SCN1A gene defect)." P Ex. 127 at 6. Claire's more recently filed medical records also indicate that her seizures have been instigated by minor illness, allergies, heat, and sunlight. P Ex. 127 at 8-9, 17, 49. The parties' experts all testified that Claire suffers from Dravet Syndrome.

III. DISCUSSION

1. Introduction

SCN1A mutations have been found as an alternate to vaccine causation in both the medical literature and by the court. See Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1381 (Fed. Cir. 2012) (affirming the undersigned's findings that their SCN1A gene mutations were solely responsible for the minors' Dravet Syndrome and that the only harm caused by vaccination was a "single, isolated initial febrile seizure"); Deribeaux v. Sec'y of Health & Human Servs., No. 5-306V, 2011 WL 6935504, at*32 (Fed. Cl. Spec. Mstr. Dec. 9, 2011) (finding that that the administration of a vaccine did not itself cause or contribute to the minor's Dravet Syndrome), aff'd, --- Fed. Cl. ---, 2012 WL 2367037 (2012)(appeal docketed August 10, 2012); Craner v. Sec'y of Health & Human Servs., No. 10-475V, 2011 WL 6401290

(Fed. Cl. Spec. Mstr. Oct. 27, 2011) (granting petitioners' request to dismiss their claim, after the minor's treating physicians indicated that that the SCN1A gene mutation was the cause of the minor's seizures). But see Snyder v. Sec'y of Health & Human Servs., 102 Fed. Cl. 305, 326 (2011) (reversing and remanding a special master's finding that the minor's Dravet Syndrome "was caused solely by a mutation in the SCN1A gene"); Harris v. Sec'y of Health & Human Servs., 102 Fed. Cl. 282, 305 (2011) (reversing and remanding a special master's finding that the minor's Dravet Syndrome "was caused solely by a mutation in the SCN1A gene").

This case presents a variation on the SCN1A issue. In this case, all testifying experts agree that Claire has an SCN1A mutation. Further, all testifying experts agree that as a result of this mutation, Claire suffers from a severe epileptic syndrome known as SMEI, or Dravet Syndrome. With this concession, it would appear that the question of vaccine causation is answered. See id. However, the twist in the instant claim is that petitioners allege that Claire's vaccinations triggered the initial symptom of her Dravet Syndrome, a seizure, at an earlier point in Claire's inevitable disease process and by doing so caused a more severe form of Dravet Syndrome. Stated another way,

> Petitioners' theory of the case is that Claire was born with a SCN1A gene mutation that predisposed her to developing seizures and cognitive problems. An environmental trigger, which in this case was Claire's September 19, 2005 vaccination, caused the onset of her seizures and cognitive problems to begin earlier and to be more severe than they likely otherwise would have been.

Petitioners' Post Hearing Brief ("P Brief") at 9. Thus, this case presents an issue of first impression.

As will be discussed below, petitioners failed to make their case. Over the course of a two-day hearing extensive testimony was taken examining very complex medical literature. In the end, the undersigned found respondent's testimony more persuasive. While recognizing the excellent qualifications of petitioner's expert neurologist, Dr. Wheless, his testimony was found to stretch the reasonable bounds of the submitted literature. There was simply no reliable evidence presented that Claire's September 19, 2005 vaccination caused her inevitable disease process to result in a worse outcome.

2. The Parties' Experts

Where "medical evidence [is] not definitive," the special master may rely heavily on expert medical testimony. Broekelschen v. Sec'y of the Dept. of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010). Expert medical testimony is particularly important in off-Table injury cases because "[t]he special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories." Id. (citing Lampe v. Sec'y of the Dept. of Health & Human Servs., 219 F.3d 1357, 1361 (Fed. Cir. 2000)). "Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." Moberly, 592 F.3d at 1325-26 (holding special masters "are entitled – indeed, expected – to make determinations as to the reliability of

the evidence presented to them and, if appropriate, as to the credibility of the persons presenting the evidence"). However, in weighing the expert testimony, the special master may not "cloak the application of an erroneous legal standard in the guise of a credibility determination, and thereby shield it from appellate review." Andreu v. Sec'y of the Dept. of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009). This case is not about the credibility of the experts - but it is a case of persuasiveness and reliability of the experts. On that score, respondent prevailed. The testifying experts in this case were all exceedingly well qualified and testified accordingly. However, the undersigned found respondent's experts far more persuasive in discussing the medicine and the issue presented in this case and relied upon their testimony in finding against petitioners. The undersigned will briefly discuss the experts' backgrounds, but for the sake of brevity will not fully detail their curriculum vitae.

a. Dr. Frances Kendall

Dr. Frances Kendall is a board certified biochemical geneticist practicing in Alpharetta, Georgia. Tr. at 12, 15. Dr. Kendall completed medical school at the University of Medicine and Dentistry of New Jersey. P Ex. 112 at 1. Dr. Kendall was a pediatric resident and a chief resident at Thomas Jefferson University Hospital and she received her genetics training as a fellow at Children's Hospital and Harvard Medical School in Boston. Tr. at 14. Dr. Kendall's primary area of practice focuses on mitochondrial disease. Tr. at 12.

b. Dr. James Wheless

Dr. James Wheless is a clinical pediatric neurologist with a specialty in epilepsy. Tr. at 106-07. Dr. Wheless directs the pediatric neurology program at the University of Tennessee, the comprehensive epilepsy program at the Neuroscience Institute and LeBonheur Children's Hospital, and pediatric neurology at St. Jude's Research Hospital. Tr. at 101. Dr. Wheless also serves as a professor at the University of Tennessee Medical School. Tr. at 104. Dr. Wheless went to medical school at the University of Oklahoma where he also completed his pediatric residency. Tr. at 101-02. He received pediatric neurology training at Northwestern University in Chicago and completed a fellowship at the Medical College of Georgia in EEG and clinical nerve physiology. Tr. at 102. Dr. Wheless is board certified in pediatric neurology, clinical neurophysiology, and pediatrics. Tr. at 103.

c. Dr. Gerald Raymond

Dr. Gerald Raymond is the director of neurogenetics at the Kennedy Kreiger Institute in Baltimore and a professor of neurology at John Hopkins School of Medicine. Tr. at 266. He attended medical school at the University of Connecticut Medical School. Id. at 267. Dr. Raymond completed his pediatric residency at John Hopkins Hospital. Id. Dr. Raymond completed a residency in neurology with a special qualification in child neurology at Massachusetts General Hospital. Id. He also completed a one year fellowship in Belgium at the Universite Catholique de Louvain doing developmental neuropathy. Id. Dr. Raymond then returned to Massachusetts General/Harvard Medical School and completed three years of training in genetics and teratology. Id. Dr. Raymond is board certified in child neurology and clinical genetics. Id.

d. Dr. Max Wiznitzer

Dr. Max Wiznitzer is a faculty member of the Department of Pediatrics at Rainbow Babies and Children's Hospital as well as a member of the Division of Neurology at the same hospital. Tr. at 430. He is also an associate professor of pediatric neurology and international health at Case Western Reserve University. Id. at 430-31. Dr. Wiznitzer attended medical school at Northwestern University. Tr. at 429-30. He completed a residency in pediatrics at Cincinnati Children's Hospital and a developmental pediatrics fellowship at Cincinnati Center for Developmental Disorders. Tr. at 430. Dr. Wiznitzer then completed three years of training in child neurology at the Children's Hospital of Philadelphia and a year two fellowship at the Albert Einstein College of Medicine after receiving a grant from the National Institute of Health. Id. Dr. Wiznitzer is board certified in neurology with special qualifications in child neurology. He is also board certified in neurodevelopmental disorders. Tr. at 431.

3. Legal Background

This claim is pursued a significant aggravation of an Off-Table injury pursuant to §11 (c)(1)(C)(i-ii) of the Vaccine Act. The Act further provides that:

> The term ''significant aggravation'' means any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health.

§33(4). The Court of Appeals for the Federal Circuit has not addressed the proper standard for demonstrating significant aggravation in an Off-Table injury claim. The Circuit did discuss significant aggravation in Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099 (Fed. Cir. 1996); however, Whitecotten involved a Table claim.[6] Given the concessions made in this claim by petitioners regarding the SCN1A mutation, as well as the narrow issue presented, the legal environment is not critical. That is that given that petitioners agree that an SCN1A mutation causes SMEI, Claire's injury, and the undersigned's finding that petitioners failed to demonstrate that an arguably earlier onset of Claire's seizures affected the outcome of her

[6] The Court of Federal Claims in Loving provided a framework for considering significant aggravation claims in off-Table claims blending the tests in Whitecotten and Althen.

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

Raybuck v. Sec'y of Health & Human Servs., No. 06-846V, 2010 WL 4860778, at *12 (Fed. Cl. Spec. Mstr. Nov. 9, 2010) (citing Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (Fed. Cl. 2009)).

condition caused by her gene mutation, it remains a given that the gene mutation was the sole cause of Claire's condition.[7]

4. Genetics Background

Given the agreement between the parties on the genetic issues presented, an extensive discussion is unnecessary. For a thorough background discussion of genetics and the SCN1A mutation See Stone v. Sec'y of the Dept. of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at *13-16 (Fed. Cl. Spec. Mstr. Apr. 15, 2010) (Stone I), rev'd on other grounds, 95 Fed. Cl. 233 (Fed. Cl. 2010), on remand, 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011), aff'd, 99 Fed. Cl. 187 (Fed. Cl. 2011), aff'd, 676 F.3d 1373 (Fed. Cir. 2012), reh'g denied, --- F.3d ---, 2012 WL 3642794 (Fed. Cir. 2012). However, for context of the later discussion, a brief primer is provided through the testimony offered by Dr. Raymond. The undersigned notes that the genetics and SCN1A mutation background information testified to by Dr. Kendall was consistent with that offered by Dr. Raymond. See Tr. at 23-29, 61-67.

a. DNA and Protein Synthesis

As an initial matter, Dr. Raymond explained "the human genome comprises our DNA as the coding or the recipe for our inherited material." Tr. at 276. DNA provides the blueprint for cellular structure and function. See, e.g., R Ex. P at 3. The process by which proteins are created from the DNA blueprint is called protein synthesis; thus, a change or mutation[8] in the

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[7] In their Post Hearing Brief, petitioners reference several sections of the Restatement of Torts as support for their claims. P Brief at 30-33 (citing Restatement (Second) of Torts §§ 431, 458, 461 and Restatement (Third) of Torts §§26, 31). The Federal Circuit has held that off-Table causation cases are to be considered "consistently with principles set forth in the Second Restatement of Torts." Stone, 676 F.3d at 1379 (citing Walther v. Sec'y of the Dept. of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007)(citing Shyface, 165 F.3d at 1352)).

Petitioners' arguments herein regarding the Restatement sections primarily address damages –what the Program would be liable for if it is found that the vaccinations significantly aggravated Claire's condition. Petitioners' use of the principles espoused in these sections is either provided for already in binding legal authority or considered in the causation finding in this Decision. Regarding the Restatement (Second) of Torts § 431, the Federal Circuit's Shyface decision already incorporates this section, providing binding authority that the vaccination must be a "substantial factor" in bringing about the alleged injury. See, e.g., Shyface, 165 F.3d at 1352-53. The remaining sections possibly implicate causation issues, which are addressed herein, or regard damages. The question of damages is not reached as the undersigned finds against petitioners regarding any causative role played by the vaccines.

In Stone, the Federal Circuit considered petitioners arguments utilizing the sections of the Restatement (Second) of Torts concerning superseding causes. Stone, 676 F.3d at 1379-82. The Federal Circuit held petitioners' arguments did not apply as the special master found the "vaccines played no role in causing either child's SMEI." Id. at 1381-82. Similarly, petitioners' arguments herein are accounted for or are in the undersigned's finding inapplicable.

[8] Mutation is defined as: "1. In genetics, a permanent transmissible change in the genetic material, usually in a single gene, although the term is sometimes used to include gross alterations in chromosomal

DNA can affect the functionality of that protein, consequently causing disease. Tr. at 299-300. Dr. Raymond described this process in great detail at the Hearing on January 20, 2012. Tr. at 276-300. See also Respondent's Trial Exhibit A ("R T Ex. A"). But essentially, the proteins formed by this process determine how cells are formed and how they function. A mutation alters normal function.

b. Mutations - Generally

Dr. Raymond discussed three different types of mutations: 1) point mutations, which consist of missense mutations and nonsense mutations; 2) deletions; and 3) insertions. Tr. at 296-97; R T Ex. A at 16. A point mutation, which is at issue in Claire's case, involves a single base pair of the DNA being replaced by another base pair. Tr. at 296. The result of this replacement may be a nonsense mutation, which codes for no amino acid during the protein synthesis process. Id. Alternatively, the substituted base pair may code for a different amino acid, which is referred to as a missense mutation. Id.[9]

Dr. Raymond explained the type of mutation that is present can affect the outcome. Tr. at 297-99; R T Ex. A at 17. A mutation may result in the coding for the same amino acid, which is referred to as silent. Id. Thus, the change in the base pair codes, for the same amino acid that was originally intended, does not affect the person's clinical presentation. Tr. at 297. Alternatively, you can have a conservative mutation that results in coding for a very similar amino acid, thus function is "close enough" to normal. Tr. at 298; R T Ex. A at 17. Changes that result in an amino acid with very different physical properties are referred to as non-conservative mutations. Id. Dr. Raymond explained that non-conservative mutations are "changing, really changing, the physiochemical properties" and can result in a "clinical manifestation." Tr. at 298-99. One may also see changes that result in "a stop codon, and so protein would stop being made there." Tr. at 299; R T Ex. A at 17. Finally, you may also see a "frameshift" that "changes [the] reading-frame position of subsequent base pairs," R T Ex. A at 17, and that changes "everything downstream." Tr. at 299.

Dr. Raymond explained that the functional effects from mutations can range from loss of function to abnormal function, even to death of the organism. Tr. at 299-300; R T Ex. A at 18. Dr. Raymond also explained that if you have a mutation, but no affect on the function of the protein, that is referred to as a polymorphism." Id. at 313; R T Ex. A at 24. A polymorphism is "seen in unaffected members of the population" where the change has a neutral effect. R T Ex. A at 24.[10]

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structure. 2. A cell, virus, or organism exhibiting such a change." Dorland's Illustrated Medical Dictionary, 1212 (32nd ed. 2012).

[9] Finally, a deletion will result from removal of a base pair, and an insertion will result from addition of a base pair. Tr. at 296-97; R T Ex. A at 16.

[10] Polymorphism is defined as: "1. The existence within a population or species of several different forms of individuals, or the occurrence of different forms or stages in an individual over time. 2. Genetic p." Dorland's Illustrated Medical Dictionary, 1490 (32nd ed. 2012).

c. The SCN1A Gene

The SCN1A gene encodes a particular structure of a neuron.[11] "Neurons, the principal cells of the nervous system, maintain an electrical potential . . . across the cell membrane at rest and use changes in [this] potential to carry information." R Ex. P at 4. A "key element[] of this gradient is the ability to control the flow of charged molecules . . . . This role is carried out by membrane channels." Id. "Membrane channels are proteins that serve as passageways for specific molecules" and may be comprised of one or several proteins. Id.

The gene at issue in Claire's case, 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." Id. Sodium is a charged molecule and "needs to be tightly regulated in the flow across the cell membrane to maintain the gradient so that the neuron may send information in an appropriate way." Id.

Three proteins comprise this sodium channel, an α subunit and two β subunits. Id. It is the α subunit that is encoded by the SCN1A gene and "is a large molecule that forms a[n] . . . opening across the membrane." Id. Dr. Raymond explained, "[i]t is important to recognize that this is not simply a hole in the fabric of the cell, but a highly complex chemical environment that allows the net passage of sodium from one side to another." Id. Dr. Raymond continued discussing the structure of the α subunit:

> it is not just a single pore, but is rather four . . . domains which are numbered by the Roman numerals - I through IV. Each of these domains is made . . . up of six segments that span the entire width of the membrane. The region between segments five and six serve as the sodium pore for each of the domains while the preceding [fourth] segment serves as the voltage responsive switch. When the voltage is at a certain level, the pores [or]space between segments five and six, 'opens' and sodium ions are allowed through.

Id. at 4-5.

Several neurologic conditions are associated with mutations of the SCN1A gene: familial hemiplegic migraines, several epilepsy syndromes, including Generalized Epilepsy with Febrile Seizures plus ("GEFS+"), and Claire's condition, SMEI. Id. This range of diseases "resulting from alterations in SCN1A rests on the structure of the channel and how the genetic mutation affects the function."[12] Id. at 5. Mutations in DNA "that affect the primary function of

[11] A neuron is defined as "any of the conducting cells of the nervous system. A typical neuron consists of a cell body, containing the nucleus and the surrounding cytoplasm (perikaryon); several short radiating processes (dendrites); and one long process (the axon), which terminates in twig like branches (telodendrons) and may have branches (collaterals) projecting along its course. The axon together with its covering or sheath forms the nerve fiber." Dorland's Illustrated Medical Dictionary, 1267 (32nd ed. 2012).

[12] As will be discussed below, part of petitioners' attack on Dr. Raymond's theory that Claire's mutation is the sole cause of her disease focuses on the variations of disease found in patients with the SCN1A mutation.

the channel such as the pore region have been demonstrated to have a more severe disease or phenotype associated with them." Id.

5. Claire's SCN1A Mutation and Dravet Syndrome

a. Claire's Mutation

Utilizing the above background information, we come to Claire's specific mutation, which Dr. Raymond and Dr. Wiznitzer opine is the **sole** cause of her condition. Again, it is important to note that Drs. Kendall and Wheless also concede that the cause of Claire's Dravet Syndrome is her mutation. The laboratory testing conducted and interpreted by Athena Diagnostics revealed that "analysis of [Claire's] SCN1A gene identified a DNA sequence variant [mutation] that has been reported in the literature to be associated with SMEI or SMEB, the severe phenotypes associated with SCN1A mutations." P Ex. 88 at 1. The report indicated that Claire's "test result is consistent with a diagnosis of, or a predisposition to developing, the severe phenotypes associated with SMEI [Dravet Syndrome] or SMEB." Id. Specifically, Claire's DNA mutation is "a [t]ransversion[13] A > T" at "[n]ucleotide [p]osition IVS14+3," P Ex. 88 at 1; as explained by Dr. Raymond this means Claire has a "transversion of A to T, adenine[14] to thymine[15] at the intervening sequence [IVS]. . . . intron No.14, . . . plus three … into the intron." Tr at 316. Dr. Raymond explained the resulting amino acid change of adenine to thymine is significant because "it's gone from a purine[16] to a pyrimidine,"[17] which is a transversion. Id. at 317. Dr. Raymond explained the significance of the location of the mutation at IVS14+3 is that this is a "highly conserved region" in a splice site. Id. This is important "[b]ecause conserved regions in the splicing site would imply that more likely than not it's going to have a significant

[13] Transversion is defined as "2. in molecular genetics, a point mutation in which a purine base replaces a pyrimidine base or vice versa." Dorland's Illustrated Medical Dictionary, 1956 (32nd ed. 2012).

[14] Adenine is defined as "1. a major purine base. In animal and plant cells it usually occurs condensed with ribose or deoxyribose to form the nucleosides adenosine and deoxyadenosine. As such, it is a component of nucleic acids, of certain nucleotides, and of many coenzymes." Dorland's Illustrated Medical Dictionary, 26 (32nd ed. 2012).

[15] Thymine is defined as "a pyrimidine base, in animal cells usually occurring condensed with deoxyribose to form the nucleoside deoxythymidine, a component of deoxyribonucleic acid. The corresponding ribonucleoside, thymidine, is a rare constituent of ribonucleic acids. Dorland's Illustrated Medical Dictionary, 1924 (32nd ed. 2012).

[16] Purine bases are defined as "a group of chemical compounds of which purine is the base, including 6-oxypurine (hypoxanthine); 2,6-dioxypurine (xanthine); 6-aminopurine (adenine); 2-amino-6-oxypurine (guanine); 2,6,8-trioxypurine (uric acid); and 3,7-dimethyl xanthine (theobromine)." Dorland's Illustrated Medical Dictionary, 202 (32nd ed. 2012).

[17] Pyrimidine bases are "a group of chemical compounds of which pyrimidine is the base, including 2,4-dioxypyrimidine (uracil), 2,4-dioxy-5-methylpyrimidine (thymine), and 2-oxy-4-aminopyrimidine (cytosine), which are common constituents of nucleic acids." Dorland's Illustrated Medical Dictionary, 202 (32nd ed. 2012).

effect on the formation of the protein."[18] Id. at 321. Dr. Raymond discussed the process of RNA splicing, Tr. 321-325, R T Ex. A at 26-29, and explained splice site mutations, which Claire possesses, are "a common cause of genetic diseases," Tr. at 324, and are "overrepresent[ed]" within genetic disorders. Id. at 325. Again, it is important to note that Dr. Kendall's testimony did not contradict the genetics background later offered by Dr. Raymond.

The Athena Lab report also indicated that Claire's "mutation arose de novo (was not inherited). This pattern of inheritance is observed in most SMEI or SMEB patients, and further increases the probability that this known disease-associated mutation could be associated with a severe phenotype" rather than a mild or normal phenotype. P Ex. 88 at 1.

b. Dravet Syndrome or Severe Myoclonic Epilepsy of Infancy (SMEI)

> Dravet Syndrome (also known as severe myoclonic epilepsy of infancy; SMEI) is characterised by onset of seizures around 6 months of age. Initial seizures are usually prolonged convulsions, either generalized or hemiclonic, often triggered by fever. Other seizure types that subsequently develop include myoclonic, partial, absence, and atonic seizures. From the second year of life, intellectual development in these infants begins to plateau or regress, resulting in intellectual disability. About 70-80% of children with Dravet Syndrome have mutations in SCN1A, of which 95% are de novo.

P Ex. 92, R Ex. MM, McIntosh et al., Effects of Vaccination on Onset and Outcome of Dravet Syndrome: a Retrospective Study, 9 Lancet Neurol. 592 (2010).

6. Analysis

As previously indicated the experts in this case all agree Claire's SCN1A genetic mutation is the cause of her disease, Dravet Syndrome. Tr. at 62 (Dr. Kendall was asked on cross-examination "in your opinion what role does the mutation play in her [Claire's] condition?" Dr. Kendall responded "[i]t's causative of her Dravet [S]yndrome."); Tr. 175-76 (Dr. Wheless was asked on cross examination: "Did Claire Barnette's SCN1A mutation cause her Dravet Syndrome?" Dr. Wheless responded "[y]eah. I mean, I think if she did not have that defect, would she have Dravet [S]yndrome? I don't think so, no. I think it's etiologically linked, yes.").

Petitioners, however, argue that Claire's vaccinations "caused the onset of her seizures and cognitive problems to begin earlier and to be more severe than they likely otherwise would have been." P Brief at 9. The undersigned finds petitioners have not demonstrated by a preponderance of the evidence that Claire's vaccinations caused a worse outcome of her condition or altered the natural course of her disease.

a. Whether Vaccination Triggered an Earlier Onset of Claire's Dravet Syndrome

[18] See Stone I at *18 (for discussion of conserved regions).

It is uncontested that the evidence demonstrates vaccinations can cause a fever which in turn can cause a seizure,[19] often the first outwardly visible manifestation or symptom of Dravet Syndrome. Tr. at 387-88. Dr. Raymond explained on cross-examination that for those with Dravet Syndrome "vaccines have a tendency to raise the temperature and they're at a developmental point in their disease process when a rise in temperature can result in seizures." Tr. at 371. Dr. Raymond indicated he was "of the opinion that [Claire] most likely had from her vaccine a mild elevation in temperature and that she had a seizure on that day because of this elevation in temperature." Tr. at 387. Thus, the parties agree that Claire's September 19, 2005, vaccination likely triggered the September 19, 2005, seizure. See also Tr. at 468 (Dr. Wiznitzer testifying that "Dr. Wheless and I agree these are known stressors [minor illness, fever] that could provoke seizures.").

Petitioners assert that not only did the September 19, 2005, vaccination cause Claire to suffer a seizure that same evening, but it also caused the onset of her Dravet Syndrome to occur earlier than it otherwise would have. To support this proposition petitioners rely upon an article by McIntosh. P Ex. 92, R Ex. MM, McIntosh et al., Effects of Vaccination on Onset and Outcome of Dravet Syndrome: a Retrospective Study, 9 Lancet Neurol. 592 (2010). McIntosh examined whether patients with Dravet Syndrome and a known SCN1A mutation expressed a "genuine temporal association of seizure onset with vaccination" and additionally whether "patients who had onset of Dravet Syndrome shortly after vaccination had any specific clinical, molecular, or outcome differences that could suggest the disorder in these patients represents a separate entity." P Ex. 92 at 2. The undersigned will first discuss the first query put forth by McIntosh, whether or not vaccination affected the onset of Dravet Syndrome.

The McIntosh authors pursued this study after they demonstrated in an earlier study that 12 of 14 patients with "presumed vaccine encephalopathy" in fact had previously unrecognized Dravet Syndrome, and 11 of those 14 had SCN1A mutations. P Ex. 92 at 5 (McIntosh discussing Berkovic). Berkovic concluded that "vaccination had been wrongly blamed as an acquired cause of a genetic disorder[, Dravet Syndrome]," thus rejecting vaccination as the "causal factor in that cohort." Id. However, the authors in Berkovic could not exclude the possibility "that vaccination triggered the onset of Dravet Syndrome . . . or resulted in a worse neurological outcome" for these SCN1A patients. Id. To address this uncertainty the McIntosh study was conducted.

McIntosh reviewed data from 95 patients with Dravet Syndrome and SCN1A mutations. P Ex. 92 at 3. Validated data indicating the date of first seizure and vaccination dates was

[19] A seizure post-vaccination may be caused by a fever, which in turn was triggered by the shots. Dr. Raymond opined that Claire most likely had a slight temperature elevation post-vaccination that triggered her initial seizure. Tr. at 387. However, there is no persuasive evidence in the record that Claire experienced a fever post-vaccination on September 19, 2005. Claire was not taken to the hospital following her September 19, 2005 seizure and the EMT records were never filed by petitioners. Petitioners' affidavits do indicate that Claire was examined by EMT who checked her vitals and reported she was "okay." P Ex. 24 at 1; P Ex. 25 at 1. Petitioners also reported to Claire's pediatrician on September 20, 2005 that Claire did not have a fever. P Ex. 4 at 21. However, there is no evidence indicating what her temperature was the evening of September 19, 2005.

available from 40 of the patients. Id. Although, it is relevant to note that the remaining 55 patients did not differ in "terms of mean age at onset, outcome, syndromic diagnoses, or mutation types." Id. The patients with validated data were broken into two groups: 1) a vaccine proximate group which included twelve patients who experienced the first seizure 0 to 1 day post vaccination; and 2) a vaccine distant group of 28 patients who experienced seizure onset 2 to 98 days post vaccination or prior to vaccination. Id.

The McIntosh analysis demonstrated that the mean age of onset of Dravet Syndrome for the vaccine proximate group was 18.4 weeks, with a standard deviation of 5.9. Id. at 4. The mean age of onset for the vaccine distant group was found to be 26.2 weeks, with a standard deviation of 8.1. Id. In sum, the authors found approximately one third of the 40 patients examined "had disease onset less than 2 days after vaccination, and the mean age at onset in these patients was significantly lower than that of patients whose disease onset was vaccination-distant." Id. at 5. Specifically, "[t]he mean age of disease onset was 7.8 weeks earlier in the vaccination-proximate group than in the vaccination distant group." Id. Accordingly, the authors found that "[v]accination **might trigger earlier onset** of Dravet [S]yndrome in children who, **because of an SCN1A mutation, are destined to develop the disease**." Id. at 1 (Emphasis added). It is important to note, as will be discussed in more detail later, McIntosh found "no evidence that vaccinations before or after disease onset affect [the patients'] outcome." Id. In fact the authors recommend that "vaccination should not be withheld from children with SCN1A mutations." Id.

Petitioners' expert geneticist, Dr. Kendall, relied on this study to conclude that Claire's vaccinations on September 19, 2005, triggered an earlier onset of her disease. Tr. at 72-73. However, Dr. Kendall indicated **she could not predict** how much earlier the onset of the disease occurred as a result of the vaccinations. Id. at 75-76. Petitioners' neurology expert Dr. Wheless, however, maintained that based on the McIntosh study Claire experienced the onset of her disease as much as two to three months earlier than she would have otherwise. Tr. at 151.

Respondent's expert geneticist, Dr. Raymond, does not dispute the study's finding regarding seizure manifestation, and agreed on cross-examination that "vaccines have a tendency to raise the temperature and they're at a developmental point in their [the vaccine proximate patients] disease process when a rise in temperature can result in seizures." Tr. at 371. However, he disputes that Claire had an earlier onset of her disease as a result of her vaccinations. Dr. Raymond testified that Claire

> doesn't have [an] earlier onset. She has onset when her genetic disorder would manifest itself, and the first clear evidence of that is a brief seizure around the time of a vaccination, but her clinical course is not altered, so the onset of her genetic abnormality is conception, and that has not been altered in any way by the vaccine.

Tr. at 386. Thus, Dr. Raymond's position is that Claire's first seizure at 6 months of age is exactly when the onset of seizures is expected to begin in a Dravet Syndrome patient. The undersigned noted that the medical literature and both parties' experts agree that 6 months is in fact the typical average onset of Dravet. See P Ex. 92 at 1 (McIntosh states "Dravet Syndrome . .

. is characterized by onset of seizures at around 6 months."); Tr. at 88 (Dr. Kendall agrees the literature reports an average onset of Dravet Syndrome at 6 months); Tr. at 183 (Dr. Wheless testified that six months "[i]t's average onset. It's a typical onset."). Dr. Raymond explained that at this point in development there is a switch from the embryonic sodium channel Nav. 1.3 to Nav. 1.1 which is the protein where the SCN1A gene mutation exists and with this switch you start temperature sensitivity and the onset of seizures. Tr. at 345-347. Respondent noted the animal models, particularly those of mice that have given scientists an understanding of Dravet syndrome. R Brief at 10-11, 23-24 (referencing R Exs QQ, WW, AAA, CCC, DDD).[20] Dr. Raymond explained on how the mouse models "recapitulate almost exactly the developmental profile of Dravet syndrome" in a human child. Tr. at 309. According to respondent's experts, these pieces of literature were used to demonstrate two significant aspects of respondents case: that a primer, such as vaccination or temperature elevation, were not necessary to induce seizures in Dravet syndrome and the fact that it is the channelopathy – the sodium channel defect caused by the mutation – that is most determinative of outcome severity, not an inconsequential environmental trigger or time of onset.

Additionally, respondent's experts point out that the onset of Claire's disease was inevitable, and did not coincide with the September 19, 2005 seizure, but rather was present at conception. Tr. at 386 (Dr. Raymond "the onset of her genetic abnormality [which caused her disease] is conception."). Dr. Wiznitzer elaborated on this point:

> The first seizure she had on September [1]9, 2005, was not the start of her epileptic encephalopathy. The start of her epileptic encephalopathy was the moment she developed the Nav. 1.1 channel of haploinsufficiency, in other words, when the wiring in her brain was not right. . . . The epileptic encephalopathy is not that you had some isolated individual seizures, it's the wiring problem with the brain . . . . The seizures are only a manifestation.

Tr. at 477-78. Dr. Wheless in fact agrees that Dravet patients "had their Dravet's since birth obviously." Tr. at 172. Further, Dr. Wiznitzer explains that even if Claire had not received a vaccination on September 19, 2005, or suffered a seizure that day, she would likely have been expected to seize following the next stressor presented. Id. at 471-72. As found by McIntosh:

> If vaccination was withheld the patients in the vaccine-proximate group would be expected to have had disease onset with the next substantial environmental trigger, be it fever, infection, or another stressor.

[20] R Ex. QQ, Ragona, F. et al, Cognitive development in Dravet Syndrome: A retrospective, multicenter study of 26 patients, 52(2) Epilepsia 386-92 (2011) (Ragona); R Ex. WW, Yu, F., et al., Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy of infancy, 9(9) Nature Neuroscience 1142 (2006); R Ex AAA, Kalume, F., et al., Reduced Sodium Current in Purkinje Neurons from NAv1.1 Mutant Mice: Implications for Ataxia in Severe Myoclonic Epilepsy in Infancy, 27(41) J of Neuroscience 11065 (2007); R Ex. CCC, Oakley, J., et al., Insights into pathophysiology and therapy from a mouse model of Dravet syndrome, 52(Supp. 2) Epilepsia 59 (2011); R Ex. DDD, Ogiwara, I., et al., Nav1.1 Localizes to Axons of Parvalbumin-Positive Inhibitory Inerneurons: A Circuit Basis for Epileptic Seizures in Mice Carrying an Scn1a Gene Mutation, 27(22) J of Neuroscience 5903 (2007).

P Ex. 92 at 6. Dr. Wiznitzer points out that Claire in fact suffered her seizure subsequent to the September 19, 2005 seizure on October 4, 2005, which coincided with a "mild illness," as reflected in the hospital medical records indicating that Claire was taking Dimetapp to treat a clear runny nose, and that she had a cough. Tr at 464-66 (citing P Ex. 6 at 3, P Ex. 5 at 4). Claire was also experiencing a mild illness consisting of a fever, cough, and runny nose when she experienced her third seizure on October 16, 2005. Tr. at 466-67 (citing P Ex. 9 at 2-3).

Finally, as explained by Dr. Raymond, Dr. Wheless is mis-utilizing the onset finding from McIntosh to opine that, but for her September 19, 2005, vaccinations, Claire would not have suffered the onset of her seizures for another two to three months. The undersigned notes as an initial matter, as respondent points out, you cannot apply "group population statistics to an individual case." R Brief at 15. As Dr. Raymond explained "you can't take the individual and say that individual seized eight weeks earlier because she's in the vaccine proximate group." Tr. at 339. Additionally, Dr. Raymond points out that Dr. Wheless ignores the low end of the range provided by McIntosh of two weeks. Id.

The undersigned finds based on the evidence presented, including the medical literature and the testimony of all the experts, that the first visible manifestation of Claire's disease — her September 19, 2005, seizure — was more likely than not triggered by her vaccination that same date. Thus, Claire's initial seizure most likely occurred earlier than it would have absent the vaccination, although as to how much earlier, the undersigned agrees with Dr. Kendall, that cannot be predicted. Tr. at 75-76. The undersigned finds it unlikely Claire's first seizure occurred significantly earlier than it would have absent her vaccinations in light of the fact that Claire's September 19, 2005, seizure occurred at six months and this is the time frame the literature indicates infants with SCN1A mutations will begin exhibiting symptoms. Ultimately, the issue of whether or not Claire's vaccination caused the onset of her disease to begin sooner than it would have absent vaccination is unimportant to resolving this case, since the evidence overwhelmingly demonstrated that Claire's condition was not made worse or aggravated by her vaccinations or September 19, 2005, seizure as discussed below.

b. Whether Vaccination Caused a More Severe Outcome in Claire's Dravet Syndrome

It is uncontested that SCN1A mutations have variability in outcome. We know that the range of outcome for SCN1A mutations includes not only Dravet Syndrome, but also "certain other epilepsy syndromes, as well as familial hemiplegic migraine." Tr. at 304. Petitioners and Dr. Wheless argue this variability is evidence that Claire's vaccinations likely worsened her disease. Tr. at 118-124. However, the evidence shows that variability in outcome is affected by the location and type of mutation. For example, some mutations are polymorphisms, which are silent and have no effect on the protein.

Claire's mutation is "a [t]ransversion A > T" at "[n]ucleotide [p]osition IVS14+3," P Ex. 88 at 1; as explained by Dr. Raymond this means Claire has a "transversion of A to T, adenine to thymine at the intervening sequence [IVS]. . . . intron No.14, . . . plus three … into the intron." Tr at 316. Based on the information currently available, this mutation has a deleterious outcome. Athena Diagnostics indicated that it is a "previously reported disease-associated mutation." P

Ex. 88 at 1. Further, the lab indicated not only is it a "disease-associated mutation," but it is "DNA sequence variant that has been reported in the literature to be associated with SMEI or SMEB, the severe phenotypes associated with SCN1A mutations." Id. Dr. Kendall indicated she was aware of at least six individuals who also had Claire's exact mutation, and who also had Dravet Syndrome. Tr. at 63; P Ex. 111 at 3. Dr. Raymond indicated the public database indicates two individuals with the exact SNC1A mutation as Claire who also have Dravet Syndrome. Tr. at 319-320 (citing Ex. RR (public database)). Dr. Raymond discussed that one infant with the exact mutation as Claire is described in the submitted medical literature as a four month old infant girl suffering also from Dravet Syndrome. Tr. at 318 (citing R Ex. GG). Accordingly, Claire's mutation is one that has been reported, studied, followed, and is known to have a severe outcome, Dravet Syndrome.

However, even without the identically reported mutations associated with Dravet Syndrome, there are additional factors that demonstrate Claire's mutation would likely be disease causing as testified to both parties' geneticists. 1) The amino acid change is significant. As explained by Dr. Raymond, a transversion has occurred in that the amino acid has gone from a purine to a pyrmidine. Tr. at 317. 2) The location of the mutation is indicative of a poor outcome because it occurred in a "highly conserved region[]in the splice sites." Id. This location indicates to a geneticist that the mutation is going to have a "significant effect on the formation of the protein." Tr. at 321. Dr. Kendall also testified splice site mutations "typically do" have a deleterious effect. Tr. at 64. 3) The part of the protein Claire's mutation affects is functionally important. Tr. 64-65 (Dr. Kendall agrees.) And additionally, as reported by Athena Diagnostics and agreed to both Drs. Kendall and Raymond, Claire's mutation arose de novo, meaning it was not inherited from her parents. P Ex. 88 at 1; Tr. at 34 (Dr. Kendall); Tr. at 314 (Dr. Raymond). As reported by Athena Diagnostics "[t]his pattern of inheritance is observed in most SMEI or SMEB patients, and further increases the probability that this known disease associated mutation could be causative of a severe phenotype." P Ex. 88 at 1.

Petitioners cite the Suls study[21] as demonstrative of the variability of SCN1A mutations and as evidence that the vaccine worsened Claire's disease course. Tr. at 46; P Brief at 21. The Suls study looked at a "4-generational Bulgarian family with 4 individuals with generalized epilepsy" and a chromosomal deletion in the SCN1A gene. P Ex. 91 at 2. It was found that the family members presented with "both moderate and severe phenotypes." Id. at 4. Dr. Raymond pointed out that one family member who was developmentally "normal" was actually a mosaic carrier of the gene, meaning he had "a mixed population of cells," all of which did not carry the alteration. The rest of the family was not developmentally normal. Tr. at 336-338. However and more importantly, the alterations involved in the family discussed in Suls were completely distinct from Claire's known disease causing variant as pointed out by Dr. Raymond. Tr. at 397-398.

As discussed at length earlier, Claire's specific genetic mutation not only possesses the characteristics expected of a disease causing alteration, but her exact mutation has been reported multiple times in other individuals expressing Dravet Syndrome. Thus, while variability is demonstrated in SCN1A mutations in general, the evidence convincingly demonstrates that

[21] P Ex. 91, Suls, A. et al., Four generations of epilepsy caused by an inherited microdeletion of the SCN1A gene, 75 Neurology 72-76 (2010)(Suls).

someone with Claire's specific mutation is more likely than not going to manifest at the severe end of the spectrum of Dravet.

Additionally, Drs. Kendall, Raymond, and Wiznitzer all agree Claire's clinical disease course followed the expected course of Dravet Syndrome children. Tr. at 90-91 (Dr. Kendall testified, putting aside Claire vaccinations, nothing about her history is inconsistent with onset and progression of Dravet's Syndrome.); Tr. at 328 (Dr. Raymond testified based on Claire's medical records and what is known of Dravet "Claire's course has followed . . . exactly what we expect from an individual who is so affected."); Tr. at 458 (Dr. Wiznitzer agreed regarding Claire's clinical course "that's clearly what is described in the [Dravet] population."). Dr. Wiznitzer described this course as follows

> [S]he had the seizure profile, clear-cut seizure profile, plus we would call them the provocations that are known to bring out seizures in the Dravet population. In addition, developmentally she did not have any major issues in about the first year of life and into the second year of life, and then the medical records tell us that there was a change where her difference from her age became more apparent in terms of her developmental progress, initially shown with her language skills, which is a classic picture for the Dravet population, that there seems to be a difference between the language compared to the motor skills that are present.

Tr. at 456. Thus, Claire's clinical history, as agreed by the parties' experts, is consistent with the typical clinical picture of Dravet, which the experts agree is caused by a mutation in the SCN1A gene.

In addition to Claire's history mirroring the expected course of Dravet, respondent's experts convincingly demonstrated through their discussion of the medical literature that immunizations do not alter outcome of Dravet Syndrome patients with SCN1A gene mutations. As discussed above, McIntosh found the vaccine proximate group experienced disease onset a mean of 7.8 weeks sooner than the vaccine distant group. However, as mentioned earlier, the second query addressed in the McIntosh was whether or not "vaccination affected the . . . outcome of the disorder." P Ex. 92 at 1. Or more specifically, "whether patients who had onset of Dravet [S]yndrome shortly after vaccination had any specific clinical, molecular, or outcome differences that could suggest the disorder in these patients represents a separate entity." Id. at 2. McIntosh recognized this was an important inquiry as "[s]uch data might have important consequences for the advice given to parents regarding vaccination." Id. The McIntosh study's findings demonstrated

> that, **although vaccination might sometimes seem to trigger** the onset of Dravet [S]yndrome, there is **no evidence** that patients in the vaccination-proximate group had a different disorder from those in the vaccination-distant group. In particular, the similarity in clinical and outcome measures between patients in the vaccination-proximate group and those in the vaccination-distant group is **not consistent** with vaccination itself affecting the severity of the disorder.
>
> . . . .

> If vaccination was withheld the patients in the vaccination-proximate group would be expected to have had disease onset with the next substantial environmental trigger, be it fever, infection, or another stressor.
>
> We therefore conclude that there is **no rational basis for withholding DTP immunization** for potentially lethal childhood diseases for fear of causing Dravet [S]yndrome or injuring the brain by a direct or presumed immune-mediated mechanism. . . . **Outcome was not influenced by vaccination** after clinical onset [], and thus vaccination does not seem to cause brain damage.[22]

P Ex. 92 at 5-6 (emphasis added). Consistent with the McIntosh authors' discussion of their study's findings above, the authors provide the following interpretation of their study:

> Vaccination **might trigger earlier onset** of Dravet [S]yndrome, in children who because of an SCN1A mutation, are destined to develop the disease. However, vaccination should not be withheld from children with SCN1A mutations because **we found no evidence that vaccinations before or after disease onset affect outcome.**

P Ex. 92 at 1 (emphasis added). The McIntosh study directly addresses the petitioners' theory in this case and the McIntosh study findings squarely reject it. Dr. Raymond discussed the data examined in McIntosh, and explains that the authors found no correlation between proximity to vaccination and intellectual outcome, intellectual regression, or type of mutation. Tr. at 344-45 (citing P Ex. 92 at 4). Dr. Wheless attempted to disagree with this study's findings, see tr. at 147, but his efforts where unimpressive as the findings are clear and unequivocal as discussed above.[23]

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[22] The authors note that "this analysis was post hoc and would ideally require confirmation in a prospective study." P Ex. 92 at 6.

[23] The undersigned notes that Dr. Kendall cited a letter from Yuval Shafir, M.D. published in response to McIntosh that was also critical of the author's conclusion. P Ex. 111 (citing P Ex. 115, 9 Lancet Neurology 1147-1148 (2010)). As noted in Deribeaux the authors' reply effectively rebuts any concerns raised in Dr Shafir's letter.

> A letter commented on the McIntosh article discussed above. Pet'r Ex. 54, Yuval Shafrir, *Vaccination and Dravet Syndrome*, 9 Lancet Neurol. 1147 (2010). The letter branded as "premature and maybe even dangerous" the conclusion in the McIntosh article that there is no data to justify withholding vaccination from children with "severe" SCN1A mutations. *Id.* at 2. Dr. Shafrir asserted that McIntosh "ignores the tendency towards severe intellectual disability in the vaccination-proximate group[.]" *Id.* Dr. Shafrir also asserted that, "Other channelopathies have also shown age-dependent vulnerability." *Id.* He posited that "seizure in the neonatal and infant brain might be more harmful developmentally than are seizures at an older age." *Id.* He suggested screening all newborns for SCN1A mutations in advance of vaccination, postponing vaccination or using prophylactic antiepileptic treatments. *Id.*

Petitioners argue that the "mere fact that the vaccination hastened the onset of the clinical manifestation of Claire's Dravet [S]yndrome shows that vaccination was a substantial factor in bringing about harm to Claire." P Brief at 36. This is plainly incorrect and was clearly rejected by McIntosh. Petitioners and Dr. Wheless are inconsistent in their use of the McIntosh article, accepting the portion of the McIntosh study that fits their theory of causation regarding onset and ignoring the finding regarding outcome that directly rejects their theory. When forced to confront the study's conclusion Dr. Wheless unconvincingly attempts to dispute it. Dr. Wheless argues "outcome is different from harm." Tr. at 194. He alleges McIntosh is looking at outcome, and you cannot measure the outcome in Dravet Syndrome patients because everyone is "severely affected, there's no category below that. I can't say the vaccine made you worse because there is no worse." Id. Dr. Wheless argues that just because McIntosh finds there was no change in outcome does not mean there was no harm, but rather that the harm cannot be measured. Id. This he calls the "floor effect." Id. at 195. This line of reasoning is rejected. As an initial matter, upon questioning by the court, Dr. Wheless conceded that the McIntosh authors are using the words "outcome" and "harm" synonymously. Id. at 197. Agreeing, "they equated no harm with the same outcome." Id. at 198. Dr. Raymond points out that the "floor effect" does not even come into play with this study because McIntosh has patients with higher functioning, as well as moderate and severe functioning. Tr. at 348-49. Additionally, as described by Dr. Raymond, McIntosh used the proper tools of independent analysis with blind assessors to ensure that a floor effect was not a concern. Tr. at 349. Finally, Dr. Raymond testified that contrary to Dr. Wheless' testimony you can assess harm, and it was looked at by McIntosh, specifically noting the finding that one indication of harm, "brain damage," was not caused by vaccinating SCN1A /Dravet syndrome patients. Tr. at 351-52.

Notwithstanding the finding by McIntosh, Dr. Wheless continued to propose that an earlier onset of Dravet Syndrome can result in a worse outcome. Unfortunately for petitioner, he was unsuccessful. In an attempt to support this position, Dr. Wheless relies on literature that is, unfortunately for petitioners, not on point.[24] Dr. Wheless testified that the O'Callaghan study

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> The authors of the McIntosh article replied to Dr. Shafrir. Pet'r Ex. 54 at 2. Among other points, the authors stated that "post-hoc analysis for severe disability versus all other cases did not reveal an effect" on severity of intellectual outcome as between vaccine-proximate and vaccine-distant patients. *Id.* at 2. "[P]erhaps our best evidence against his assertion is our data for children vaccinated after disorder onset, in whom no effect or negative trends regarding regression or intellectual outcome were seen." *Id.* They noted as "very unlikely," the suggestion that some asymptomatic individuals "escape" developing DS, despite having a deleterious mutation, because, "The missense mutations and mutations resulting in protein truncation that are seen in children with Dravet syndrome have not been found in healthy controls." *Id.* at 3.

Deribeaux, 2011 WL 6935504, *21.

[24] P. Ex. 126, O'Callaghan, F., et al., The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: Evidence from the United Kingdom Infantile Spasms Study. 52(7) Epilepsia 1359-1364 (2011) (O'Callaghan); P. Ex. 125, Woolf, A., et al., Update on the Clinical Management of Childhood Lead Poisoning, 54 Pediatr. Clin. N. Am. 271-294 (2007)

supports his theory that "epileptic encephalopathies that start in the first year of life in general are bad, but the younger you get with those, usually the worst your outcome is." Tr. at 139. However, O'Callaghan is discussing infantile spasms. P Ex. 126 at 1. Dr. Wheless argues this study is applicable because it, like Dravet Syndrome is an epileptic encephalopathy of infancy. However, as explained by Dr. Wiznitzer "you cannot apply the findings of the O'Callaghan 2011 paper to Dravet Syndrome. You can only apply it to infantile spasms. . . . infantile spasms are a totally different creature." Tr. at 501. "Once you stop the [infantile] spasms with treatment . . . the encephalopathy is gone." Id. at 503. "It's time limited." Id. Dr. Wiznitzer explained in contrast "Dravet Syndrome is an epileptic encephalopathy, but it never stops . . . because the sodium channel abnormality is always present." Tr. at 505-06. Dravet kids, testified Dr. Wiznitzer, just get "worse and worse developmentally," tr. at 506, from the "second year or after. And that's long after the seizure . . . Dravet [S]yndrome has started. In infantile spasms, the problems with cognition are immediate." Tr. at 508. As Dr. Wiznitzer testified Dr. Wheless is "comparing apples and oranges." Id. at 507. The undersigned notes the same problem is present with Dr. Wheless' use of the Woolf article which discusses lead poisoning, not Dravet Syndrome. As Dr. Wiznitzer testified "it's not relevant, it's totally not relevant. Lead poisoning is a totally different brain damage problem than Dravet [S]yndrome." Id. at 515.

Dr. Wheless also relied on the Shields article to support his position that an earlier onset caused a worse outcome for Claire. Shields, Dr. Wheless testified, supports the proposition that "seizures themselves lead to mental retardation." Tr at 141 (citing P Ex. 122). As an initial matter there is no evidence that Claire's one minute seizure on September 19, 2005 seizure caused mental retardation. Dr. Wiznitzer also pointed out that the "wiring abnormalities" discussed in Shields are not present in individuals with Dravet as demonstrated by pathology studies. Tr. at 511-12 (citing R Ex. YY).[25] [26] Further, the Shields article discusses various types of epilepsies, SMEI is described, but a finding specific to early onset of seizures and a worse

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(Woolf); P. Ex. 122, W. Donald Shields, Catastrophic Epilepsy in Childhood, 41 (Suppl. 2) Epilepsia S2-S6 (2000).

[25] R Ex. YY, Catarino, C. et al., Dravet syndrome as epileptic encephalopathy evidence from long-term course and neuropathy, 134 Brain 2982-3010 (2011) (Catarino).

[26] In addition to Shields, Dr. Wheless relied on a review of animal models by Holmes to support his theory that an earlier onset of seizures caused a worsening of Claire's condition. Tr. at 118-119 (citing P Ex. 95, Holmes, G., Effects of Seizures on Brain Development: Lessons from the Laboratory, 33 Pediatr. Neurol. 1-11 (2005) (Holmes)). Holmes discusses that "seizures early in life can result in permanent behavioral abnormalities and enhance epileptogenicity." P Ex. 95 at 1. However, the models discussed by Holmes were not specific to Dravet Syndrome, and did not discuss the implications of an SCN1A gene mutation. Interestingly, Holmes noted a limitation to the models in that there were none that mimic Dravet Syndrome. Id. at 7. There are now mouse models that do mimic Dravet as discussed supra at 16. Additionally, Catarino rebuts Holmes and Shields as testified to by Dr. Wiznitzer. Catarino found that "[o]verall we have not identified any histopathological hallmark of Dravet syndrome. In fact, a striking feature was the conspicuous preservation of neurons and interneurons, including within the hippocampus, and cortex in the frontal, temporal and occipital regions, despite decades of poorly controlled seizures." Tr. at 513 (citing R Ex. YY at 27). Dr. Wiznitzer explained that Catarino demonstrates that "you can't claim there's direct damage to the brain in that manner from seizure activity. It has to be that the channelopathy is a significant contributing factor here." Id.

outcome in the disease process is not discussed. Additionally, as Dr. Wiznitzer pointed out on direct examination the Shields article is over 10 years old and was published prior to the link being recognized between SCN1A genetic mutations and Dravet Syndrome. Tr. at 509-511. Such literature should not be relied upon when there is more recent and on-point literature discussing this issue.[27]

In addition to McIntosh, respondent relies upon several other studies to support her contention that age of onset does not affect either the level of harm or the outcome for Dravet Syndrome patients with a SCN1A mutation. In Ragona,[28] a 2011 retrospective study the authors, including Charlotte Dravet, examined "the role of epilepsy and genetic background in determining the cognitive outcome of patients with Dravet [S]yndrome." R Ex. QQ at 1. Ragona found

> The variability of outcome, and the appearance of neurologic deficits hardly ascribable to epileptic activity . . . suggest that the channelopathy [mutation] itself is probably crucial in determining the phenotype. The role of channelopathies in inducing symptoms other than seizures is well documented . . .

Id. at 6. The authors, like McIntosh, found that "[s]tatistical analysis failed to detect any significant correlation between severity of cognitive impairment and the following clinical variables: age at onset . . . ." Id. at 5. The authors conclude that "epilepsy phenotype contributes in determining cognitive development" and that "the early appearance of myoclonus and/or absences might have a negative prognostic impact." Id. at 6. Which as respondent notes, "may recognize some potential for an association in Dravet syndrome patients between seizure type and cognitive impairment, [but] it is not evidence of a *causal* association between the two." R Brief at 24 (emphasis in original). The point at issue here however, as discussed by Dr. Raymond, is that the authors "say very clearly that much of this seems to relate to the channelopathy itself." Tr. at 411. Likewise, Dr. Witznitzer points out that Ceulmans[29] found

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[27] Finally, with their Post Hearing Reply Brief filed on August 23, 2012, petitioners filed an "Itemization of Seizure Events" labeled Appendix A. This itemization appears to be a log of seizures noted in Claire's medical records and her mother's journal. P Reply Brief at 6. Petitioners present this information to show the number of seizures Claire suffered during the time petitioners allege she would have been seizures free but for the September 19, 2005, vaccinations. Id. Dr. Wheless had discussed the two to three seizures noted in records during Claire's hospitalization during this time and Dr. Wiznitzer discussed ten seizures Claire suffered in the eight weeks post vaccination. See, e.g., P Reply Brief at 6. The undersigned notes that there were no seizures in between the first one suffered the evening of September 19, 2005 and the next seizure that was temporally associated with an upper respiratory illness on October 4, 2005. P Ex. 6 at 3, P Ex. 5 at 4. Even the next seizure was associated with another mild illness. P Ex. 9 at 2-3. The significance of this number of seizures, as tallied by petitioners, was not directly discussed by the experts. As the undersigned and petitioners' attorney are not medical experts, not much can be gleaned from this new assertion.

[28] R Ex. QQ, Ragona, F. et al, Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients, 52(2) Epilepsia 386-92 (2011) (Ragona).

[29] R Ex. U, Ceulemans, B., Overall management of patients with Dravet syndrome, 53(Suppl. 2) Dev. Med. Child Neurol. 19-23.

that after studying four children with Dravet Syndrome that there "is a strong argument favoring the genetic disorder itself as probably being the most important factor for developmental problems in these children." R Ex. U at 4.

As discussed above, there is no reliable evidence that Claire's vaccinations caused a more severe outcome of her Dravet Syndrome or significantly aggravated her condition in any way. To the contrary, the evidence presented demonstrates that vaccination does not affect outcome for Dravet patients.

Finally, in finding respondent's position more persuasive, petitioners' contentions are necessarily rejected. First, it is noted that Dr. Kendall gives minimal support to petitioners' contention that earlier onset equates to a worsened condition. First, Dr. Kendall opines that based on McIntosh she believes Claire's onset occurred earlier than it would have absent the vaccination, as to how much earlier she testified she cannot predict. Tr. at 75-76. However, Dr. Kendall agrees Claire's onset is at six months, which she also agrees is the average age of Dravet onset according to the literature. Tr. at 90. Dr. Kendall, however, indicates she has no opinion regarding whether Claire's seizure on September 19, 2005, rather than some later date, resulted in a worse outcome for Claire – on this point Dr. Kendall chooses to defer to a neurologist. Tr. at 32, 79.

It is also noted that Claire's treating doctors do not ascribe in the medical records any role for her vaccinations in her condition. This includes Dr. Wheless who has treated Claire from July 27, 2010, through at least the date of the hearing in this case. P Ex. 127 at 48; Tr. at 558. His medical records indicate that while he was aware of the temporal association between her vaccination and onset of her seizures and her SCN1A mutation, Dr. Wheless never commented in any way as to a possible aggravating effect of her vaccines to her genetic condition. P Ex 127 at 5-13, 16-18, 45-51. When asked about this oddity in the records on cross-examination, Dr. Wheless gave no meaningful explanation. Tr. at 565-68. Petitioners' counsel did point out that Dr. Wheless did hold the opinion of vaccine causation in his expert reports beginning on August 2, 2010. Id. at 568-69. However, that does not answer the question as to why, as Claire's treating physician, Dr. Wheless took the position that the SCN1A mutation was causing Claire's condition without noting in any way that the vaccine worsened the condition.

In the final analysis, this case involves complex medical issues. However, when reduced to its most basic level, the decision to deny petitioners' claim is relatively simple. The experts agree that the SCN1A gene mutation is the cause of Claire's Dravet syndrome. While there is variability in the outcome of SCN1A mutations, Claire's specific mutation has been reported to likely result in severe disease, Dravet Syndrome. The experts agree that Claire's clinical disease course followed the expected course of Dravet Syndrome. The average age of onset of Dravet Syndrome is six months, which is when Claire experienced her first seizure. Vaccines may trigger an earlier manifestation of Dravet; however, if Claire's Dravet Syndrome occurred earlier due to her immunizations, there is no clinical evidence relied upon by petitioners' experts supporting petitioners' contention that it worsened her expected medical course. In fact Dr. Kendall stated that nothing about Claire's history is inconsistent with the onset of Dravet's Syndrome. Tr. at 90-91. Drs. Raymond, Wiznitzer, and Wheless agreed. See supra at 19. Thus, Dr. Wheless attempted to make a case for worsening by reference to the medical literature. That

effort, as discussed above, was entirely unpersuasive. In summary, this complex medical case was actually not complex to decide. There was no evidence of worsening and Dr. Wheless' efforts to find worsening through the medical literature failed. Claire is undoubtedly a severely impacted child, supported by loving parents, all of whom the undersigned had the pleasure of meeting. The vaccination, however, played no role in her condition.

IV. CONCLUSION

As discussed above, the issue presented in this case was a narrow one - essentially boiling down to whether or not Claire's first seizure, likely triggered by her September 19, 2005, vaccination caused her Dravet Syndrome to be worse than it otherwise would have been. Petitioners have failed to demonstrate that Claire's vaccinations altered or aggravated the course of her pre-existing genetic condition resulting in a worse outcome of Claire's disease. While all the experts who testified were well qualified, the undersigned finds the testimony offered by respondent's experts to be a far more persuasive interpretation of the scientific literature, the medical records, and the specific clinical evidence regarding Claire's genetic mutation. The overwhelming evidence presented demonstrates that Claire's specific SCN1A mutation was the sole cause of her disease and that her vaccinations did not result in any worsening of that disease process.

In conclusion, based on the record as a whole, and as discussed above, the undersigned finds that petitioners have failed to meet their burden of proof and entitlement is **denied**. The Clerk of Court shall enter judgment accordingly.

IT IS SO ORDERED

s/Gary J. Golkiewicz
Gary J. Golkiewicz
Special Master