In the United States Court of Federal Claims

No. 07-59V
VACCINE CASE
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TO BE PUBLISHED[1]

JED SNYDER and LILIA SNYDER, Parents of N.S., a Minor Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Alternative Causation; Causation-In-Fact; National Childhood Vaccine Injury Act of 1986, 42 U.S.C. § 300aa-12(e)(2); Pre-Existing Condition.

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MEMORANDUM OPINION AND FINAL ORDER

This case arises from a Motion to Review a July 21, 2011 Decision Denying Compensation in *Snyder* v. *Sec'y of HHS*, No. 07-59V, 2011 WL3022544 (Spec. Mstr. Fed. Cl. July 21, 2011) ("*Snyder*").

[1] Pursuant to Rule 18(b) of the Vaccine Rules of the United States Court of Federal Claims ("VRCFC"), this Memorandum Opinion and Final Order was filed under seal on November 28, 2011 and "held for 14 days to afford each party the opportunity to object to the public disclosure of any information furnished by that party." VRCFC 18(b).

I. RELEVANT FACTS.[2]

A. Medical Records.

N.S. was born on [redacted]. Pet. Ex. 4 at 3. In January 2005, during a two-month well child visit N.S. received a set of immunizations, including a DTaP[3] vaccination, without exhibiting any adverse results. Pet. Ex. 5 at 13, 17. Throughout March 2005, N.S.'s examinations reflected that he was a healthy baby and continued to develop normally. Pet. Ex. 27 ¶ 6; *see also* Pet. Ex. 4 at 259.

On March 4, 2005, during his routine four-month well child visit N.S. received a second DTaP vaccination. Pet. Ex. 5 at 4, 17. Around 6:00 a.m. the next morning, N.S.'s mother awoke and observed N.S. experiencing jerking movements in his right arm that spread to other parts of his body. Pet. Ex. 27 ¶ 8. Within five minutes, N.S.'s entire body started convulsing, he lost focus, blinked and twitched his eyes, and stared into space. Pet. Ex. 27 ¶ 8. His mother measured his temperature at 99 degrees using the underarm method. Pet. Ex. 27 ¶ 8. Around 6:30 a.m., N.S. was taken to the Emergency Room at St. Rose Dominican Hospital in Las Vegas, Nevada. Pet. Ex. 27 ¶ 8.

The Admissions Record stated: "Seizure disorder[.] Acute life[-]threatening event[.] Post vaccination syndrome[.]" Pet. Ex. 4 at 254. Initially, N.S.'s temperature was 98.6 degrees, but over the next five hours it rose to 100.9 degrees. Pet. Ex. 4 at 246. Thereafter, his left arm and leg continued twitching for approximately thirty minutes, before stopping without medical intervention. Pet. Ex 4 at 246. The Emergency Room doctor described N.S. as having a "febrile illness/possible focal seizure vs[.] infantile spasms." Pet. Ex. 4 at 246.

At St. Rose Dominican Hospital, N.S. underwent a series of tests. The results of a computed tomography ("CT") scan were normal. Pet. Ex. 4 at 323-24; Pet. Ex. 6 at 19-20. Cerebrospinal fluid ("CSF"), blood, and urine tests were also all negative. Pet. Ex. 4 at 306-12; Pet. Ex. 6 at 19-20. No electroencephalogram ("EEG")[4] was conducted at this time. N.S. remained in the hospital for three days until March 7, 2005, and was released with instructions to follow up with a neurologist. Pet. Ex. 4 at 261.

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[2] The relevant facts herein were recited in *Snyder*, 2011 WL3022544 at **1-4 as derived from: Petitioners' Appendix of Exhibits (Pet. Exs. 1-100); Respondent's ("Government") Appendix of Exhibits (Gov't Exs. A-WW and Gov't Trial Ex. 1); and an Evidentiary Hearing held before the Special Master on October 8-9, 2009 ("TR 1-594").

[3] DTaP is the acronym for the "diphtheria and tetanus toxoids and acellular pertussis vaccine." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 568 (32nd ed. 2011) ("DORLAND").

[4] An EEG is "a recording of the potentials on the skull generated by currents emanating spontaneously from nerve cells in the brain. . . . Fluctuations in potential are seen in the form of waves, which correlate well with different neurological conditions and so are used as diagnostic criteria." DORLAND at 600.

Later on March 7, 2011, N.S. was examined by Dr. Sri Halthore, M.D., a pediatric neurologist at Neurology Specialists in Las Vegas, Nevada. Pet. Ex. 6 at 19-20. After reviewing N.S.'s history, Dr. Halthore concluded that N.S. suffered a "[s]ingle seizure, rather prolonged. This could have been a febrile seizure[5]. . . . The seizure was several hours after getting the [DTaP] shot." Pet. Ex. 6 at 19-20. Dr. Halthore recommended careful observation and an EEG, but did not prescribe any medication. Pet. Ex. 6 at 20. Dr. Halthore also had "a long conversation with [N.S.'s] parents about seizures, and also the relationship between vaccines and seizures." Pet. Ex. 6 at 20.

During March 2005, N.S. exhibited diminished energy levels, decreased appetite, and his left arm often stiffened and turned inward with a clenched fist. Pet. Ex. 27 ¶ 12.

On April 6, 2005, during a trip with his family to Colombia, N.S. experienced a second seizure lasting approximately 10 seconds. Pet. Ex. 27 ¶ 13. He was treated and diagnosed with an afebrile seizure. Pet. Ex. 23 at 2[6]. On April 20, 2005, an EEG was performed in Bogotá, Colombia, and interpreted as normal. Pet. Ex. 23 at 1, 7. An examination with a pediatric neurologist noted that N.S. had "low muscle tone, especially in the upper body and left arm, and displayed uncoordinated movements when active[.]" Pet. Ex. 27 ¶ 14; *see also* Pet. Ex. 23 at 1-2. Physical therapy was recommended. Pet. Ex. 23 at 2.

On April 27, 2005, after returning to the United States, N.S. had a follow-up visit with Dr. Halthore, during which an EEG was performed. Pet. Ex. 6 at 21. The EEG was normal. Pet. Ex. 6 at 21. Dr. Halthore recommended medication in the event that N.S. experienced future seizures and N.S. was referred for a magnetic resonance imaging ("MRI") scan of his brain. Pet. Ex. 6 at 21. On May 10, 2005, the MRI scan was performed and reported as normal. Pet. Ex. 17 at 1-2.

On May 17, 2005, N.S. received a third DTaP vaccination. Pet. Ex. 5 at 11, 17. On May 26, 2005, N.S. suffered a third seizure episode, lasting almost two minutes and affecting his right arm and leg.[7] Pet. Ex. 27 ¶ 15. Dr. Halthore started N.S. on phenobarbital[8] and diagnosed N.S.

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[5] A febrile seizure is a series of "convulsions associated with high fever, usually seen in infants and children." DORLAND at 411 (definition of "febrile convulsions").

[6] Pet. Exs. 23-25 are in Spanish and were never translated by the Special Master. The court, however, has obtained a translation.

[7] There is some discrepancy in the record as to the correct date of N.S.'s third seizure. Dr. Daniel Miles's notes contain a typographical error stating that the third seizure occurred on "May 215, 2005." Pet. Ex. 7 at 1. The Expert Reports of Drs. Kinsbourne and Raymond, however, indicate that the third seizure occurred on April 26, 2005. Pet. Ex. 32 at 1; Gov't Ex. C at 1. The record is consistent in stating that this seizure lasted two minutes and involved twitching of the right arm and leg, however. *Compare* Pet. Ex. 7 at 1 *with* Pet. Ex. 32 at 1.

[8] Phenobarbital is "a long-acting barbiturate, used as a sedative, hypnotic, and anticonvulsant." DORLAND at 1428.

as having epilepsy. Pet. Ex. 27 ¶ 15; Pet. Ex. 6 at 27. On July 6, 2005, N.S. suffered a fourth seizure lasting 8 minutes and was taken to the New York University Medical Center's Emergency Room. Pet. Ex. 7 at 1; *see also* Pet. Ex. 10 at 54.

On July 14, 2005, N.S. was evaluated by Dr. Daniel Miles, M.D., a Pediatric Neurologist at New York University Comprehensive Epilepsy Center. Pet. Ex. 7 at 1. Dr. Miles diagnosed N.S. a having "partial seizures with motor delays," and recommended the continued use of Phenobarbital and participation in an Early Intervention Program. Pet. Ex. 7 at 4.

On July 21, 2005 and August 9, 2005, N.S. again experienced seizures. Pet. Ex. 6 at 27. On August 10, 2005, an additional evaluation revealed moderate to significant delays in cognition, adaptive, gross and fine motor, and speech development. Pet. Ex. 15 at 21-22. On August 15, 2005, during a physical therapy evaluation, N.S. exhibited decreased muscle tone and strength of his postural muscles and presented with 25% delays, so that "[a]t a corrected age of 8.5 months, N.S.'s average age equivalent is 6.3 months." Pet. Ex. 15 at 28. Therapeutic intervention was recommended. Pet. Ex. 15 at 28.

On August 24, 2005, N.S. suffered four seizures, beginning in the morning and progressing through the day, resulting in two separate admissions to the NYU Medical Center Emergency Room. Pet. Ex. 10 at 17.

From August 24 through August 26, 2005, Dr. Miles conducted a 48-hour video EEG. Pet. Ex. 7 at 5-6. Although no seizures were recorded, several "high amplitude, right frontal spikes" were recorded. Pet. Ex. 7 at 5-6. The EEG was "consistent with bilateral frontal cortical hyper-excitability." Pet. Ex. 7 at 5-6. The NYU Medical Center's Discharge Summary noted that "[s]eizure onset was at 4 months of age the day after vaccines were administered. . . . [N.S.] now presents with an increase in seizure frequency[.]" Pet. Ex. 7 at 7.

On September 30, 2005, N.S. had a Prevnar vaccination. Pet. Ex. 5 at 9.

Over the next several months, N.S. suffered seizures on: October 1, 2005; November 7, 2005 (twice) [9]; December 17, 2005 (when N.S. lost unconsciousness); December 21, 2005; and January 7, 2006.[10] Pet. Ex. 4 at 19; Pet. Ex. 9 at 5-7, 21-22, 41-42, 51-52.

[9] A November 8, 2005 report by Dr. Halthore recorded that N.S. experienced a seizure after immunization and that N.S. had 5-6 seizures between October 1, 2005 and November 8, 2005. Pet. Ex. 6 at 13. The report states that these seizures were "after immunization." Pet. Ex. 6 at 13. It is unclear whether the immunization referenced was N.S.'s Prevnar immunization given on September 30, 2005, Pet. Ex. 5 at 9, one day before the October 1, 2005 seizure, or his DTaP vaccination on March 4, 2005. There is no contention in this case that the Prevnar immunization affected N.S.'s disorder.

[10] A January 5, 2006 physical therapy assessment noted that, "[e]very time he had anew [sic] seizure and his seizure medication was increased, N.S. would go backwards with his gross motor skills and would have to work to catch back up to his skill level prior to the seizure." Pet. Ex. 22 at 7.

On February 21, 2006, N.S. was examined by Dr. Donald Olson, M.D., a Neurologist at Stanford University. Pet. Ex. 8 at 1-4. Dr. Olson's impression was that N.S. had symptomatic epilepsy of unclear etiology.[11] Pet. Ex. 8 at 3. He further stated:

> Of course, the question of the vaccination is important since the seizures appeared to start the day after vaccination. This is always difficult to prove or disprove. It is a question that comes up often. . . .
>
> His parent**s** and I discussed that his prognosis for normal development and seizure control is not as good as for a child who is developing normally and whose seizures are easily controlled with one medication. Therefore, I would label him as having a "guarded" prognosis.
>
> With regard to whether it is okay for vaccinations, I really do not think there is a medical contraindication,[12] though I think it very reasonable to skip the pertussis vaccination, as this is such a potent social concern even if we do not have clear scientific evidence of its causality.

Pet. Ex. 8 at 3.

On May 6, 2006, N.S. was admitted to St. Rose Dominican Hospital in Las Vegas for an episode of Status Epilepticus.[13] Pet. Ex. 4 at 40; Pet. Ex. 14 at 4. Dr. Kshama Dapthary noted that N.S.'s first seizure occurred the day after his 4-month shots, which included a DTaP shot, and another seizure occurred after his third dose of DTaP. Pet. Ex. 4 at 56.

N.S. was then transferred to the University Medical Center in Las Vegas, where he was evaluated by Dr. Alfreda Maller, M.D., a Pediatric Neurologist. Pet. Ex. 14 at 4. While there, N.S. had an EEG that showed **"**abnormal results, caused by diffuse swelling over the base[14] and activity consistent with diffuse encephalopathy vessels and postical slowing." Pet. Ex. 14 at 4. Dr. Maller decided to request genetic testing of the SCN1A gene[15] to rule out Severe Myoclonic

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[11] Etiology refers to "the causes or origin of a disease or disorder." DORLAND at 652.

[12] A contraindication is "any condition . . . which renders some particular line of treatment improper or undesirable." DORLAND at 410.

[13] "Status Epilepticus" refers to "any prolonged series of similar seizures without return to full consciousness between them." DORLAND at 1767. These seizures can be convulsive, *i.e.*, general tonic-clonic, which is serious and life-threatening, or non-convulsive, which is serious, but not usually life-threatening. *Id*. N.S.'s Status Epilepticus was of the convulsive variety. *See* Pet. Ex. 4 at 40 (describing N.S.'s seizure as general tonic-clonic).

[14] The base of the brain refers to "the inferior surface of the brain, including the undersurfaces of the cerebrum, cerebellum, and brainstem." DORLAND at 202.

[15] The SCN1A gene codes for the pore region of sodium channels in neurons, i.e. for the portion of the sodium channel responsible for controlling the transport of sodium molecules

Epilepsy of Infancy ("SMEI"), also known as Dravet's Syndrome.[16] Pet. Ex 14 at 57. This testing showed that N.S. had a DNA mutation in the SCN1A gene that is "associated with SMEI or SMEB, the severe phenotypes[17] associated with SCN1A mutations. . . . [The] result is consistent with a diagnosis of, or predisposition to developing, SMEI[18] or SMEB." Pet. Ex. 13 at 4; *see also* Pet. Ex. 14 at 73.

After a follow-up appointment, Dr. Maller wrote to N.S.'s pediatrician:

> I had the pleasure of following N.S. in a child neurology clinic on 08/04/06. As you know, he is an almost two-year-old child with intractable seizures which, so far, did not have a clear etiology. During his last hospitalization at UMC Hospital, I did send genetic testing for severe myoclonic epilepsy of infancy – Dravet's syndrome which is associated with sodium channel mutation. The result

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across cell membranes in the neurons. TR at 434-36, *see also* Gov't Ex. C at 3-4. To be specific, it codes for the $Na_v1.1$ protein, TR at 436, of the voltage-gated $\alpha 1$ subunit of the sodium channel. Gov't Ex. C at 3. As such, "[t]he SCN1A is the major component of [the sodium] voltage-gated channel. . . ." TR at 435.

[16] SMEI is a severe seizure disorder that appears during the first year of life. NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, DRAVET SYNDROME INFORMATION PAGE, http://www.ninds.nih.gov/disorders/dravet_syndrome/dravet_syndrome.htm (last visited Nov. 19, 2011). Initially, seizures are frequently febrile, *i.e.*, fever-related, though as the disorder progresses other types of seizures occur, including myoclonic seizures. *Id.* Status Epilepticus also may occur. *Id.* The child experiences cognitive impairment, developmental delays in language and motor skills, hyperactivity, and difficulty relating to others, *id.*, although development initially is normal. TR at 61. SMEI is considered to be on a spectrum of disorders with borderline severe myoclonic epilepsy of infancy (SMEB) and generalized epilepsy with febrile seizures plus (GEFS+) disorders. TR at 63, 201.

SMEB is similar to SMEI except persons with this disorder "lack several of the key features of SMEI such as myoclonic seizures and generalized spike-wave activity[.]" Pet. Ex. 46 at 844; s*ee also* TR at 61, 197.

"As defined, GEFS+ is a heterogeneous epilepsy syndrome that is characterized by febrile seizures . . . that persist beyond the age of six years, or afebrile seizures exhibiting various phenotypes including generalized epilepsy as well as partial epilepsy." Gov't Ex. NN at 180. GEFS+ is more common and is considered a less severe disorder than SMEI, in large part because GEFS+ does not result in developmental delays. TR at 61-62.

[17] A "phenotype" is "the observable morphological, biochemical, and physiological characteristics of an individual, either in whole or with respect to a single or a few traits, as determined by a combination of the genotype and the environment." DORLAND at 1431.

[18] Specifically, N.S. was found to have a mutation in a highly conserved region that codes the pore of the sodium channel in certain neurons. TR at 442-46. This mutation resulted in a change in amino acids from tryptophan to arginine. TR at 442, *see also* Pet. Ex. 13 at 4. The effect of this mutation is discussed below.

> of the test revealed that N.S. has DNA sequence variant sodium channel SCN1AG associated with a disease. I think with the clinical picture of severe intractable seizures, most often triggered by fever or vaccination, which is typical for this neurological condition, there is positive diagnostic test is confirmatory for diagnosis of the Dravet's syndrome [*sic*].

Pet. Ex. 26 at 14.

Thereafter, N.S. continued to be treated by Dr. Maller for Dravet's Syndrome and to experience developmental delay through at least June 2009. Pet. Ex. 26 at 6-13; Pet. Ex. 65 at 1-19; Pet. Ex. 87 at 1-12.

In a June 8, 2007 affidavit, N.S.'s mother, Lilia Snyder, recalled that N.S. had experienced approximately 70 seizures from his birth to that date. Pet. Ex. 27 ¶ 18.

B. Petitioners' Medical Expert Testimony: Dr. Marcel Kinsbourne.

Dr. Marcel Kinsbourne graduated from Oxford University Medical School in England in 1955. Pet. Ex. 33 at 1. From there he embarked on a distinguished career in the field of Pediatric Neurology: from 1964 to 1967 he served as a Lecturer at Oxford University; from 1967 to 1974 he was Associate Professor in pediatrics and in neurology at Duke University Medical Center; and from 1974 to 1980 he was Professor of Pediatrics at the University of Toronto Medical School. TR 9-10; *see also* Pet. Ex. 33 at 2. In 1981 Dr. Kinsbourne left his position at the University of Toronto and became Director of the Behavioral Neurology Department at the Eunice Kennedy Shriver Center, where he focused on research into developmental disabilities. TR 10-11; Pet. Ex. 33 at 2. In 1995, Dr. Kinsbourne became a Professor of Psychology at the New School University in New York City, where he teaches neuroscience to graduate students. TR at 11; Pet. Ex. 33 at 2. He has published approximately 400 articles and 8 or 9 books. TR at 13; Pet. Ex. 33 at 5-38. Currently he serves on the Editorial Board of 12 publications. Pet. Ex. 33 at 3. He is a member of numerous professional societies. Pet. Ex. 33 at 4. And, over the course of his career, Dr. Kinsbourne has won numerous awards, Pet. Ex. 33 at 2, including one awarded by the New School in 2008 for excellence in teaching. TR at 12.

Dr. Kinsbourne's opinion is that a SCN1A mutation is a "genetic susceptibility *factor* for seizure disorders," including SMEI, but there must be a "gene-*environment* interaction" for SMEI to occur. Pet. Ex. 32 at 5 (emphasis added).[19]

[19] For this conclusion, Dr. Kinsbourne cites: CASPI (2006) (Pet. Ex. 39) at 583 ("Gene-environment interactions occur when the effect of exposure to an environmental pathogen on a person's health is conditional on his or her genotype."); BURGESS (2005) (Pet. Ex. 38) at 51 ("[P]henotypes are complex emergent properties that are influenced by dynamically changing environments[.]"); *see also* Pet. Ex. 32 at 7 (citing KIMURA (2005) (Pet. Ex. 48) at 425 ("[T]he existence of genetic or environmental factors other than SCN1A mutation may modify SMEI phenotypes . . . different genetic backgrounds and/or environmental factors may critically affect the clinical features of patients with SNC1A mutations."); MULLEY (2005) (Pet. Ex. 52) at 538 (research "suggesting that other factors, genetic, and/or environmental are contributing [factors]

Dr. Kinsbourne specifically identified the pertussis component of the DTaP vaccine as an environmental agent, even in its current endotoxin-free acellular formulation,[20] that can invoke a neurological seizure response. Pet. Ex. 32 at 4, 8.[21]

In other words, "[t]here is no one-to-one relationship between SMEI and SCN1A mutation." Pet. Ex. 32 at 6.[22] For this reason, the fact that parents of children with SCN1A mutations "harbor the same genetic abnormality," but have no symptoms of a seizure disorder

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to the more severe SMEI phenotype"); BURGESS (2005) (Pet. Ex. 38) at 53 ("The degree to which these genetically initiated phenotypes are shaped by environmental influences is unclear, but it may be significant."); OTTMAN (2005) (Pet. Ex. 55) at 1530 ("Both gene-gene and gene-environment interaction[s] . . . are likely to be important in many complex diseases."); WALLACE (2005) (Pet. Ex. 61) at 11149 ("The fact that similar mutations cause two different phenotypes implies that other environmental or genetic factors are associated with SMEI.")).

[20] In an April 1, 2010 Post-Hearing Report, Dr. Kinsbourne states that the whole cell and acelluar vaccines contain comparable amounts of pertussis toxin in order to "stimulate immunity to the wild strain of Bordatella pertussis, which causes whooping cough . . . . [I]n the course of the manufacturing of the acelluar pertussis vaccine, steps are taken to inactivate pertussis toxin," but seizures can occur. Pet. Ex. 98 at 1. For this reason, Sanofi Pasteur, the manufacturer of Daptacel and Adacel have a warning label that states: "if seizures occurred within three days following the vaccination, 'careful consideration' is called for of the risks versus benefits of administering the vaccine again on a future occasion. . . . Contraindications, under which they list 'events [that] contraindicate the use of any pertussis containing vaccine,' they include 'encephalopathy within 7 days of preceding dose' and 'uncontrolled epilepsy.'" Pet. Ex. 98 at 1-2 (citing CDC-sponsored Advisory Committee on Immunization Practices (Morbidity and Mortality Weekly Report – MMWR, December 15, 2006) ("Convulsions with or without fever, occurring within 3 days after pediatric DTP/DTaP")). In support, Dr. Kinsbourne cited CYR (2001) (Pet. Ex. 91) reporting "that toxoided pertussis toxin can spontaneously revert to the active toxic state." Pet. Ex. 98 at 2. In addition, GOMEZ (2007) (Pet. Ex. 95) at 3311, reports that, even in acelluar pertussis vaccine "'some residual PTx activity may likely be present because of the limitations of the detoxification processes used.'" Pet. Ex. 98 at 2 (GOMEZ (2007) (Pet. Ex. 95 at 3311)).

[21] *See also* Pet. Ex. 32 at 7-8 (citing RHODES (2004) (Pet. Ex. 56) at 11151: ("[T]he sodium channel defect creates the initial seizure predisposition, but the concomitant excitotoxicity is the direct cause for other neurological features of the disorder"); WALLACE (2005) (Pet. Ex. 61) at 19: ("[P]erhaps the sodium channel defect creates the initial seizure predisposition, but concomitant excitotoxicity is the direct cause for other neurological features of SMEI.")).

[22] *See also* Pet. Ex. 32 at 6 (citing HARKIN (2007) (Pet. Ex. 46) at 850 (Table 3); CEULEMANS (2004a) (Pet. Ex. 40); FUJIWARA (2006) (Pet. Ex. 43); OTTMAN (2005) (Pet. Ex. 55) at 1531; TURNBULL (2005) (Pet. Ex. 60)).

evidences the necessity of an environmental factor for SMEI to manifest.[23] Of course, in this case, as Dr. Raymond noted, "there is no indication in the available records [that N.S.'s] parents were tested" for the presence of a SCN1A mutation. Gov't Ex. C at 2.

Moreover, if SMEI was solely caused by the presence of the SNC1A variant or "purely genetically driven," the introduction of DTP would not be significant, *i.e.*, there would be "no difference in the probability of seizure onset after DTP[,] as compared to [a] control [group]." Pet. Ex. 32 at 8. The National Childhood Encephalopathy Study (1981) (Pet. Ex. 35) (NCES), however, found a "significantly greater incidence of prolonged febrile seizures with onset within three days of DPT vaccination." Pet Ex. 32 at 9. Consequently, Dr. Kinsbourne concluded "there is an interaction between a genetic susceptibility factor and the DTP vaccin[e]." Pet. Ex. 32 at 9.

Dr. Kinsbourne proffered two theories as to how the pertussis component of the DTaP vaccine can trigger a seizure. First, the body's fever reaction "may induce neurochemical changes that lower the seizure threshold[.]" Pet. Ex. 32 at 11 (citing CEULEMANS (2004b) (Pet. Ex. 40)). Second, the pertussis toxin either may induce excitotoxicity of neurons leading to their "death" or inability to transmit messages to the brain,[24] or the toxin may attach to a neuron's membrane, interfering with the G protein receptors that control sodium channels.[25] Pet. Ex. 32 at 11; *see also* TR at 28.

In other words, "[t]he mutation alone does not predict the form the seizure disorder would take, its severity, the timing of its onset, or even that seizures would necessarily occur. Modifying factors resulting in causation or significant aggravation must exist. Based on the evidence . . . the modifying factors include DTP vaccination." Pet. Ex. 32 at 10.

Based on the aforementioned, Dr. Kinsbourne concluded:

> It is my opinion, to a reasonable degree of medical probability, that the DTaP vaccination that N.S. received on March 4, 2005, made a significant contribution to the causation of his severe [SMEI].

Pet. Ex. 32 at 12.

[23] Pet. Ex. 32 at 7 (citing ANNESI (2003) (Pet. Ex. 36); GENNARO (2003) (Pet. Ex. 45); NABBOUT (2003) (Pet. Ex. 53); FUKUMA (2004) (Pet. Ex. 44); and KIMURA (2005) (Pet. Ex. 48)).

[24] As discussed in RHODES (2004) (Pet. Ex. 56) and WALLACE (2005) (Pet. Ex. 61).

[25] MENKES (2005) (Pet. Ex. 51) at 633.

C. Government's Expert Testimony: Dr. Max Wiznitzer And Dr. Gerald V. Raymond.

1. Dr. Max Wiznitzer.

Dr. Wiznitzer graduated from Northwestern University Medical School in 1977. Gov't Ex. B at 1. Afterwards, he attended a four-year training program at Cincinnati Children's Hospital, followed by a Child Neurology Fellowship at the University of Pennsylvania and a two-year National Institutes of Health Fellowship studying disorders of higher cortical functioning. TR at 180-81; Gov't Ex. B at 1-2. He is board certified by the American Board of Pediatrics in Pediatrics and board certified by the American Board of Psychiatry and Neurology both in Neurology, with a Special Competence in Child Neurology, and in Neurodevelopment of Disabilities. TR at 180; Gov't Ex. B at 5. He is also a member of several professional societies, has published about 50 publications, and is a reviewer for a variety of medical journals, including serving on the Editorial Board of LANCET NEUROLOGY and THE JOURNAL OF CHILD NEUROLOGY. TR at 181-83; Gov't Ex. B at 5-6, 12-22. Dr. Wiznitzer is currently employed at the Rainbow Babies and Children's Hospital in Cleveland, Ohio, where he has an active clinical practice treating children with seizure disorders, including several with Dravet's Syndrome or GEFS+. TR at 185; Gov't Ex. B at 3. Dr. Wiznitzer has a special interest in Dravet's Syndrome and attended the first international workshop on Dravet's Syndrome held shortly before the October 8-9, 2009 evidentiary hearing in this case. TR at 188-89.

Dr. Wiznitzer's April 29, 2008 Expert Report stated that "[t]here is no evidence that the immunizations administered on 3/4/05 caused or aggravated N.S.'s epilepsy." Gov't Ex. A at 3. Rather, N.S. has "[SMEI], which has been shown to have a genetic basis (abnormality of the SCN1A gene) and is not caused by pertussis immunization." Gov't Ex. A at 3. From there Dr. Wiznitzer itemized the reasons why Dr. Kinsbourne's opinion was "flawed and has no biological plausibility:" Gov't Ex. A at 3.

1. N.S.'s medical records reflect a "diagnosis [of] Dravet syndrome or [SMEI] and clearly detail the presence of myoclonic seizures." Gov't Ex. A at 3 (citing Pet. Ex. 26 at 6-12). "Therefore, the diagnosis is not SMEB or SMEI-B." Gov't Ex. A at 3.

2. Medical literature does not "comment" on "whether the fever associated with the first seizure in SMEI was the first fever experienced by the child. . . . [I]t has been demonstrated that a modest rise in temperature (such as placement in a hot bath) is sufficient to provoke a seizure[.]" Gov't Ex. A at 3 (citing OGUNI (2001) (Gov't Ex. S)). Moreover, since "'epileptogenic' is defined as 'inducing or tending to induce epilepsy,' . . . the only 'epileptogenic effect' is the impact of the SNC1A gene mutation on the function of the SNC1A sodium channel." Gov't Ex. A at 3 (quoting MERRIAM-WEBSTER'S MEDICAL DICTIONARY (no edition given)).

3. "[G]ene abnormality does not require a 'trigger.' . . . Rather, it will *always* cause dysfunction of the SCN1A sodium channels and *result* in abnormal neuronal function and the clinical picture of SMEI[.]" Gov't Ex. A at 4 (emphasis added).

4. The "NCES data are not applicable in this case," because "N.S. received [a] DTaP vaccine [not DTP, the vaccine studied by NCES]" and other "explanations that were not associated with DTP . . . were identified . . . . [And, a]ll children with febrile seizures were normal on followup." Gov't Ex. A at 4.

5. There is no data to support Dr. Kinsbourne's view that there is an association between SCN1A mutation and several severe epilepsies of infancy that may offer a marker for children. Gov't Ex. A at 4.

6. "SMEI is genetically determined." Gov't Ex. A at 4. "[L]ater research" by DEPIENNE (2006) (Gov't Ex. I), GENNARO (2006) (Gov't Ex. L), and MORIMOTO (2006) (Gov't Ex. P) provides an explanation for why parents of children that develop SMEI do not have disorders, while the child does, *i.e.*, it is explained by the concept of parental mosiacism.[26] Gov't Ex. A at 4.

   The articles relied on by Dr. Kinsbourne to support his argument that there is gene-environment interaction for SMEI, do not support Dr. Kinsbourne's conclusions. Gov't Ex. A at 5 (discussing articles by KIMURA (Pet. Ex. 48), MULLEY (Pet. Ex. 52), OTTMAN (Pet. Ex. 55), and HARKIN (Pet. Ex. 46)).

7. NIETO-BARRERA (2000) (Pet. Ex. 54) and YAKOUB (1992) (Pet. Ex. 62) do not evidence a causal relationship between DTP and the onset of SMEI, because "neither study is a true epidemiologic study of SMEI. Secondly, since neither group of authors knew about the proven causal relationship between SMEI and SCN1A gene abnormalities, their discussions about hypothetical seizure mechanisms are outdated and obsolete. Thirdly, the articles discuss DTP, not DTaP, vaccine the latter having inactivated pertussis toxin. Fourthly, both groups admit that fever is associated with clonic seizures in children." Gov't Ex. A at 5-6.

8. Dr. Kinsbourne's criticism of BERKOVIC (2006) (Gov't Ex. E) for not referencing NIETO-BARRERA (2000) (Pet. Ex. 54) or NCES or IOM reports is incorrect. Gov't Ex. A at 6. More importantly, Dr. Kinsbourne failed to accurately describe BERKOVIC (2006) (Gov't Ex. E), wherein the authors state "the role of vaccinations as a significant trigger for encephalopathy is unlikely for several reasons . . . less than half our patients had documented fever with their first seizure, which indicates that fever is not essential . . . individuals with such mutations seem to develop SMEI and SMEB whether or not they are immunized in the first year of life." Gov't Ex. A at 6 (quoting BERKOVIC (2006) (Gov't Ex. E)).

[26] Mosiacism is "the presence in an individual of two or more cell lines that are karyotypically or genotypically distinct and are derived from a single zygote." DORLAND at 1181. In other words, as explained by Dr. Wiznitzer, "the parent has cell populations with and without the SCN1A mutation (so the parent does not have the total burden of the genetic abnormality) and, because the germ cells (single cells – sperm or egg) have the mutation, transmit the full epilepsy syndrome SMEI to the child." Gov't Ex. A at 4.

9. Dr. Kinsbournes's theory that the "pertussis toxin uncouples the G protein from the receptor, blocking the receptor's normal inhibitory control and allowing glutamate-induced excitoxicity to have free rein . . . is purely speculative and, in part, dependent on the presence of functional pertussis toxin in DTaP (in which the toxin is inactivated.)" Gov't Ex. A at 7. Moreover, none of the references "deal with in vivo neuronal inhibition or excitation." Gov't Ex. at 7. In addition, "children with SMEI (and its associated SCN1A mutation) always manifest the disorder since (1) fever is not necessary for the occurrence of the seizure and (2) the mild rise in body temperature associated with seizure occurrence cannot be avoided . . . and will occur in every child." Gov't Ex. A at 8.

Therefore, Dr. Wiznitzer's opinion was:

1. While SCN1A mutations can be *associated* with different seizure disorders, there is no evidence that "environmental factors" such as pertussis vaccination "precipitate the most severe disorder in the spectrum, SMEI". Mosaicism explains the occurrence of SMEI in a child and less severe seizure disorder in the parent.

2. Immunizations are not necessary or causal factors and their avoidance does not alter the natural history of SMEI. Therefore, DTP or DTaP are not factors in the causation of SMEI.

3. Dr. Kinsbourne's hypothesis on the action of pertussis toxin on neurons is not a biologically plausible mechanism of injury in children with SMEI.

4. While fever can be associated with seizures in SMEI, it is not a "mechanism of injury" but, rather, a factor that does not alter the evolution of the epilepsy or influence the adverse cognitive outcome.

Gov't Ex. A at 9 (emphasis added).

2. Dr. Gerald V. Raymond.

Dr. Raymond graduated from the University of Connecticut Medical School in 1984. Gov't. Ex. D at 1. Thereafter, he was an intern and Junior Assistant Resident in Pediatrics at Johns Hopkins Hospital and a Resident in Neurology at Massachusetts General Hospital. Gov't Ex. D at 1. He was then awarded research fellowships in Developmental Neuropathy at Universite Catholique de Louvain in Brussels, Belgium, and in Genetics and Teratology at Massachusetts General Hospital. Gov't Ex. D at 1. In addition, Dr. Raymond is board certified by the American Board of Psychiatry and Neurology in Neurology, with a Special Qualification in Child Neurology, and board certified by the American Board of Medical Genetics in Clinical Genetics. Gov't Ex. D at 10; TR at 394. Dr. Raymond testified that he is among the four or five physicians in the United States with dual certification in Neurology and Genetics. TR at 394. In addition, Dr. Raymond is a reviewer for a number of publications, a member of several professional societies, regularly gives lectures on neurogenetics, has published approximately 70

articles in peer-reviewed journals, and has authored more than a dozen chapters in books. TR at 397-98. Currently, he is employed as the Director of Neurogenetics at the Kennedy Krieger Institute in Baltimore, Maryland and is an Associate Professor of Neurology at Johns Hopkins Medical School. TR at 391-92. At Kennedy Krieger, approximately 75% of Dr. Raymond's time is devoted to clinical research. TR at 392. The remainder of this time is mostly spent on assisting in the diagnosis and treatment of patients, and Dr. Raymond estimates that he has consulted with two or three patients who have evidenced Dravet's Syndrome. TR at 392, 395-96. At Johns Hopkins he teaches both neurology and genetics. TR at 393.

Dr. Raymond acknowledged that SCN1A mutations have been associated with a variety of neurological conditions, but "[i]t is *not necessary* to invoke environmental or even other genetic factors in such varied phenotypic expression. Rather the type and position of the mutation with subsequent effect on the function of the protein is sufficient to have very divergent conditions." Gov't Ex. C at 5. For example, if a mutation is *de novo, i.e.*, spontaneous, as most SCN1A mutations resulting in SMEI have been found to be, that is a "powerful indicator" that the mutation is "disease causing." Gov't Ex. C at 4. Specifically, if the SCN1A mutation affects the primary function of the sodium channel, such as the pore region, the mutation likely will have a more severe phenotype associated with it. Gov't Ex. C at 4. Similarly, if the mutation is in a conserved region, then that demonstrates the importance of that region to subsequent function. Gov't Ex. C at 5. The nature of the amino acid switch, *i.e.*, its size and chemical properties, also determines the effect. Gov't Ex. C at 5.[27]

In N.S.'s case, his mutation resulted in a substitution of the amino acid[28] tryptophan[29] to arginine,[30] so that "there are clearly differences in the size and basic chemical properties between the two amino acids which would be expected to impact the protein function." Gov't Ex. C at 5.

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[27] In a March 17, 2009 Supplemental Report, Dr. Kinsbourne does not dispute that mosaicism was first recognized in MORIMOTO (2006) (Gov't Ex. P). He instead argues that MORIMOTO did not conclude that children with a SCN1A mutation who experience SMEI, but whose parents are asymptomatic, are explained by mosaicism; instead, that study concludes that "the possibility of mosaicism cannot be excluded." Pet. Ex. 80 at 1. Of more significance is the fact that whether N.S.'s SCN1A mutation was the result of mosiacism or not is irrelevant to Dr. Kinsbourne's "opinion as to a significant contribution of vaccines to causation in the case[] of . . . N.S." Pet. Ex. 80 at 1.

[28] "Amino acid" is "any organic compound containing an amino . . . and a carboxyl . . . group." DORLAND at 60. These two amino acids are among the 20 amino acids "from which proteins are synthesized by formation of peptide bonds during ribosomal translation of messenger RNA." *Id*.

[29] "Tryptophan" is "an essential amino acid . . . existing in proteins . . . necessary for optimal growth in infants and for nitrogen equilibrium in human adults. It is a precursor of serotonin." DORLAND at 1975.

[30] "Arginine" is "a nonessential amino acid . . . produced by the hydrolysis or digestion of proteins. It is one of the hexone bases and supplies the amidine group for the synthesis of creatine." DORLAND at 131.

For this reason, the spectrum of disorders associated with the SCN1A mutation is explained by non-environmental factors. Gov't Ex. C at 5. Moreover, where a parent and a child both have a SCN1A mutation, but the child presents with a more severe disorder than the parent, the explanation is not environmental, but mosiacism. Gov't Ex. C at 5-6.

Like Dr. Wiznitzer, Dr. Raymond also critiques some of the empirical studies cited by Dr. Kinsbourne to establish a causal relationship. For example, as to YAKOUB (1992) (Pet. Ex. 62), the authors do not state which vaccinations preceded severe epilipsies, nor do they describe the vaccinations as "triggering event[s]." Gov't Ex. C at 6. As to NIETO-BARRERA (2000) (Pet. Ex. 54), Dr. Raymond notes methodological problems arising from the study's retrospective nature and lack of information as to whether the patients had an SCN1A mutation. Gov't Ex. C at 6. In addition, Dr. Raymond noted that NIETO-BARRERA undermines Dr. Kinsbourne's view that the epilepsy-causing effect of the pertussis vaccine is unlikely to be due to fever alone, because NIETO-BARRERA shows that patients had a variety of illnesses before their first seizure, making it apparent that a mild fever from any source can trigger a seizure. Gov't Ex. C at 6. Dr. Raymond adds, however, that a fever is not a necessary event. Gov't Ex. C at 6. In fact, Dr. Raymond states that "individuals with [SMEI] go on to have a variety of seizures unrelated to fever." Gov't Ex. C at 6. Dr. Raymond also disputes Dr. Kinsbourne's critique of BERKOVIC (2006) (Gov't Ex. E), because Dr. Kinsbourne failed to "acknowledge the substantial literature which calls into question the conclusions of the NCES" study on which Dr. Kinsbourne relied. Gov't Ex. C at 6.

In addition, Dr. Raymond challenged Dr. Kinsbourne's G-protein theory. Although G-proteins can be affected by pertussis toxin, Dr. Kinsbourne cites, and Dr. Raymond found, no literature supporting a specific theory of "direct interaction between G-protein coupled receptors and voltage-gated sodium channels[.]" Gov't Ex. C at 7.

In addition, Dr. Raymond declined to adopt Dr. Kinsbourne's argument regarding the toxoiding process,[31] because:

> There has been no evidence in the medical literature of an environmental modifier or any interaction between mutations in SCN1A and immunizations. In addition, there is no evidence that any of the diseases or toxins that the immunizations protect against interact with SCN1A.

Gov't Ex. C at 7.

Dr. Raymond's opinion is "to a reasonable degree of medical certainty . . . N.S. . . . has [SMEI] . . . secondary to a mutation in his SCN1A gene. This is the sole cause of his epilepsy syndrome, including his subsequent developmental delay. It was not caused nor exacerbated by any of the immunizations that he received." Gov't Ex. C at 7.

[31] A "toxoid" is "a modified or inactivated bacterial exotoxin that has lost toxicity but retains the properties of combining with, or stimulating the formation of, antitoxin." DORLAND at 1943. Toxoiding is the process by which the toxicity is removed. *See* TR at 23-27 (Dr. Kinsbourne discussing toxoids and the toxoiding process).

II. PROCEDURAL HISTORY.

On January 24, 2007, a Petition For Compensation was filed in the United States Court of Federal Claims that alleged that N.S. developed SMEI as a result of his four-month DTaP vaccination. The case was assigned to Special Master Laura D. Millman.

On April 11, 2007, Petitioners filed N.S.'s medical records. Pet. Exs. 1-25. On May 22, 2007, additional medical records were filed. Pet. Ex. 26.

On June 11, 2007, Petitioners filed an Amended Petition, as well as an Affidavit signed by N.S.'s mother, Lilia Snyder. On July 6, 2007, Petitioners filed a CD containing three medical articles. Pet. Exs. 29-31.

On August 1, 2007, the Special Master filed Samuel F. Berkovic et al., *De novo mutations of the sodium channel gene* SCN1A *in alleged vaccine encephalopathy: a retrospective study*, 5 LANCET NEUROLOGY 465-66, 488-92 (2006), a medical article. Court Ex. 1.

On October 16, 2007, the Government filed its required Rule 4(c) Report.

On February 25, 2008, Petitioners filed the Expert Report and Curriculum Vitae of Dr. Marcel Kinsbourne, M.D. The next day, February 26, 2008, Petitioners filed 29 medical articles. Pet. Exs. 34-62.

On May 19, 2008, the Government filed the Expert Reports and Curricula Vitae of Dr. Max Wiznitzer, M.D., and Dr. Gerald Raymond, M.D. That same day the Government filed 18 medical articles. Gov't Exs. E-V.

On June 13, 2008, Petitioners filed a Motion To Transfer And/Or Consolidate this case with *Harris* v. *Sec'y of HHS*, No. 7-60V, because the issues presented in both cases were similar, the same attorneys represented the parties, and both parties had the same expert witnesses. For these reasons, Petitioners argued that consolidation would be expedient, judicially efficient, and minimize use of resources. On June 27, 2008, the Government filed a Response.

On July 3, 2008, Chief Special Master Golkiewicz granted Petitioners' Motion To Transfer and this case was reassigned to Special Master Christian Moran.

On July 7, 2008, the Government filed the Supplemental Expert Report of Dr. Wiznitzer, together with four medical articles. Gov't Exs. W, Y-AA.

On December 30, 2008, Petitioners filed a second Motion To Transfer And Consolidate this case with other pending cases in which Petitioners alleged that the DTaP vaccine caused Dravet's Syndrome, including: *Hammitt* v. *Sec'y of HHS*, No. 07-170V; *Stone* v. *Sec'y of HHS*, No. 04-1041V; and *Santini* v. *Sec'y of HHS*, No. 06-725V. In addition, Petitioner requested that these cases be transferred to then Chief Special Master Golkiewicz.

On January 6, 2009, the Government filed a Response. On January 9, 2009, Chief Special Master Golkiewicz issued an Order denying the December 30, 2008 Motion To Transfer And Consolidate.

On January 6, 2009, and again on February 24, 2009, Petitioners filed updated medical records. Pet. Exs. 63-79. On March 18, 2009 Petitioners filed the Supplemental Export Report of their expert witness, Dr. Kinsbourne.

On April 24, 2009, the Government filed a Supplemental Export Report of their expert witness, Dr. Raymond.

On September 1, 2009, Petitioners filed three additional medical articles. Pet. Exs. 81-83. On September 2, September 8, and September 14, 2009, Petitioners filed updated medical records of N.S. Pet. Exs. 84-88.

On September 23, 2009, the Government filed an additional medical article. Gov't Ex. CC.

On October 5, 2009, the Government filed a trial exhibit containing a PowerPoint presentation to be used by Dr. Raymond in conjunction with his testimony. Gov't Trial Ex. 1. On October 13, 2009, the Government filed an additional 16 medical articles. Gov't Exs. DD-SS.

On October 8-9, 2009 an evidentiary hearing was conducted by Special Master Moran. Those testifying included: Petitioners' expert, Dr. Kinsbourne, as well as the Government's experts, Dr. Wiznitzer and Dr. Raymond.

On November 4, 2009, Petitioners submitted nine additional medical articles. Pet. Exs. 89-97.

On December 18, 2009, the Government submitted Supplement Expert Reports from Dr. Raymond and Dr. Wiznitzer, in response to the medical literature submitted by Petitioners on November 4, 2009.

On April 5, 2010, Petitioners filed a Responsive Expert Report by Dr. Kinsbourne, including two additional medical articles. Pet. Ex. 98 Tabs A-B.

On May 24, 2010, the parties submitted Post-Hearing Memoranda. On that same day the Government filed an additional medical article, the MCINTOSH article (Pet. Ex. VV), that was not published at the time of the Evidentiary Hearing, but that Dr. Wiznitzer discussed during his testimony. TR at 257.

On July 19, 2010, the parties submitted Response Memoranda. In addition, Petitioners filed the Supplemental Expert Report of Dr. Kinsbourne, M.D., together with medical literature. Pet. Ex. 99 Tab A.

On September 22, 2010, Special Master Moran ordered the Government to file an additional article mentioned in the OAKLEY article (Gov't Ex. CC) and for Petitioners to respond, within 30 days thereafter. On September 24, 2010, the Government filed the YU article. Gov't Ex. WW. On December 16, 2010 Petitioners filed a Response.

On May 27, 2011 Special Master Moran issued a decision that was reissued on July 21, 2011, denying compensation to the Petitioners, determining that N.S.'s seizure disorder "was caused solely by a mutation in the SCN1A gene." *Snyder* v. *Sec'y of HHS*, No. 07-59V, 2011 WL 3022544 at * 36 (Spec. Mstr. Fed. Cl. July 21, 2011).

On June 27, 2011, Petitioners filed a timely Motion For Review of the May 27, 2011 Entitlement Decision in the United States Court of Federal Claims. On July 27, 2011 the Government filed a Response.

III. DISCUSSION.

A. Jurisdiction And Standard Of Review.

Section 300aa-12(e) of the Vaccine Act authorizes the United States Court of Federal Claims to review the decision of a special master. *See* 42 U.S.C. § 300aa-12(e)(2) ("The United States Court of Federal Claims shall have jurisdiction[.]"). The same section also authorizes the court, in reviewing a decision of a special master, to (1) "uphold findings of fact and conclusion of law," (2) "set aside any findings of fact or conclusion of law . . . found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," or (3) "remand the petition to the special master for further action in accordance with the court's direction." *Id*.

Findings of fact by a special master are to be reviewed under an "arbitrary and capricious standard;" legal conclusions are reviewed under a "not in accordance with law standard;" and discretionary rulings are reviewed for "abuse of discretion." *Saunders* v. *Sec'y of HHS*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) (internal quotations omitted). The United States Court of Appeals for the Federal Circuit has held that "[i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines* v. *Sec'y of HHS*, 940 F.2d 1518, 1528 (Fed. Cir. 1991). It is not the role of a court "to reweigh the factual evidence, or to assess whether the Special Master correctly evaluated the evidence." *Lampe* v. *Sec'y of HHS*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (internal quotations omitted); *see also Porter* v. *Sec'y of HHS*, 2010-5162, __ F.3d.__, __, 2011 WL 5840315 (Fed. Cir. Nov. 22, 2011).

B. The Special Master's May 27, 2011 Entitlement Decision.

On May 27, 2011, Special Master Moran issued an Entitlement Decision that began his "analysis-Causation" by assuming "that the Snyders have met their burden of establishing that the [DTaP] vaccination can affect seizure disorders," but then concluded that the "key dispute" in the case is whether an identified SCN1A gene mutation caused N.S.'s SMEI disorder. *Snyder*, 2011 WL 3022544 at * 12.

After a lengthy discussion, Special Master Moran concluded that "[t]he evidence overwhelmingly favors a finding that [N.S.'s] epilepsy was caused solely by a mutation in the SCN1A gene." *Id.* at *36. Accordingly, Special Master Moran determined that Petitioners were "not entitled to compensation" under the Vaccine Act. *Id.* at *37.

To support the conclusion that the SCN1A gene mutation was the sole cause of N.S.'s SMEI disorder, the Special Master relied on Dr. Raymond, who the Special Master considered to be "the most qualified expert to express an opinion." *Id.* at *14. According to the Special Master, N.S.'s mutation arose *de novo* in a highly conserved region of the human genome that codes the pore of the sodium channel.[32] ***Id.*** at *15. Furthermore, cases reported in CLAES (2003) (Gov't Ex. F) and OHMORI (2002) (Gov't Trial Ex. 1) evidence that other children with the same mutation also developed SMEI. *Id.* at *15 (citing TR at 217-22, 443).

The Special Master rejected the Petitioners' argument that numerous articles indicate that an environmental trigger is necessary to cause symptoms. *Id.* at *17. Instead, the Special Master found that a "more accurate generalization is that some authors have suggested that environmental factors *may* influence how a genetic mutation manifests clinically." *Id.* at *17 (emphasis added); *see also id.* at **17-21 (discussing BERKOVIC (2006) (Gov't Ex. E); SELL (2006) (Pet. Ex. 57); NIETO-BARRERA (2000) (Pet. Ex. 54); RHODES (2004) (Pet. Ex. 56); WALLACE (2005) (Pet. Ex. 61); BURGESS (2005) (Pet. Ex. 38); KIMURA (2005) (Pet. Ex 48); GAMBARDELLA (2009) (Pet. Ex. 81); DEPIENNE (2008) (Pet. Ex. 83); LOSSIN (2008) (Pet. Ex. 82); CLAES (2009) (Gov't Ex. FF); and YAKOUB (1992) (Pet. Ex. 62)). In sum, the Special Master determined that "the Snyders should have presented persuasive evidence that environmental factors influence the expression of the SCN1A gene[,]" but they did not. *Id.* at *21.

The Special Master also found the testimony of Dr. Kinsbourne regarding SCN1A unpersuasive, because Dr. Kinsbourne did not have experience treating patients with SCN1A defects, he stopped practicing pediatric neurology in 1981, and his current position is as a Professor teaching psychology to non-medical students. *Id.* at *21-22. In contrast, the Government's experts had extensive experience studying neurological problems associated with genetic abnormalities, including Dravet's Syndrome and GEFS+, and they concluded that the SCN1A gene was the cause of N.S.'s epilepsy. *Id.* at *22 (citing TR 185-86, 209-10 (Dr. Wiznitzer); TR 395-96 (Dr. Raymond)). In addition, the Special Master found that their opinions were supported by the medical literature. *Id.* (discussing BERKOVIC (2006) (Gov't Ex. E); CEULEMANS (2004a) (Pet. Ex. 40); and CLAES (2009) (Gov't Ex. FF)). In particular, the Special Master was persuaded by MCINTOSH (2010) (Gov't Ex. VV), stating that the DTaP

[32] "A *de novo* mutation is much more likely to present a severe disease[.]" *Id.* at *15 (citing MULLEY (2005) (Pet. Ex. 52)). In addition, "conserved regions" are genetic sequences that appear in other species and are thought to be important, "because their continued presence suggests that a species could not function without the particular genetic sequence." *Id.* (citing TR at 430, 444-45, 507, 556-58; DEPIENNE (2008) (Pet. Ex. 83), MULLEY (2005) (Pet. Ex. 52)). Finally, "the pore is an important location in a voltage-gated channel[,]" and "[a]lmost all mutations that have been found in the pore region of the sodium channel have been found in cases of SMEI." *Id.* (citing TR at 440-46, 512-13; Gov't Trial Ex. 1 at 28-30).

vaccine does not affect the outcome of patients that have both Dravet's Syndrome and a SCN1A mutation. *Id.* at *23.

Finally, the Special Master discounted N.S.'s treating doctors' linkage of the vaccine and the disorder. *Id.* at *23-24. First, the Special Master determined the treating doctors only presented a sequence in which the vaccine preceded the initial seizure and did not address causal connection. *Id.* at *24. Second, three of the four treating doctors had no knowledge of N.S.'s genetic mutation. *Id.* at *24. In addition, statements made by Dr. Maller after the genetic testing, referring to the vaccine triggering the initial seizure, do not indicate whether N.S. would have experienced seizures whether or not he received the DTaP vaccination, nor if the vaccine-induced seizures made N.S.'s symptoms worse. *Id.* at **24-25 (discussing Pet. Ex. 26 at 14).

The Special Master concluded that "the SCN1A mutation was solely responsible for causing [N.S.'s] epilepsy [and] resolves this case. This finding necessarily implies that the DTaP vaccine *did not affect* [N.S.'s] epilepsy." *Id.* at *25 (emphasis added).

Having addressed the role of the SCN1A mutation, the Special Master next turned to Petitioners' evidence regarding DTaP vaccine and seizure disorders. *Id.* The Special Master decided that, even if the SCN1A mutation was not the sole cause of the disorder, Petitioners still would need to establish by a preponderance of the evidence a medical theory causally connecting a significantly worsened condition to the vaccine. *Id.* The Special Master, however, found the two medical theories advanced by Petitioners "lacked clarity." *Id.*

Regarding Petitioners' argument that the DTaP vaccine can affect cells in the central nervous system, making seizures more likely, the Special Master examined the "three discrete propositions" subsumed in this theory. *Id.* at *26. The first proposition is that the lack of complete toxoiding leaves some dangerous pertussis toxin in the acelluar pertussis vaccine. *Id.* at *27 (citing TR at 25-27, 154-55). The Special Master thought that this discussion would be better informed by someone with pharmacology expertise. *Id.* He also thought it was problematic that there was no testimony on the articles that supported Dr. Kinsbourne's opinion. *Id.* Therefore the Special Master found that the evidence on this point "was not presented well" and that it made "little sense to address whether the toxoiding process completely inactivates all pertussis toxin." *Id.*

The second proposition is that the pertussis toxin can cross the blood-brain barrier, which Dr. Kinsbourne argued could happen when a fever increases the permeability of the barrier. *Id.* (citing TR at 353, 360). The Special Master found that the evidence on this point "seems to be about the same as the evidence in *Moberly*[,]" because Petitioners did not present any evidence "shor[ing] up" this argument, but "just [presented] Dr. Kinsbourne's unsupported assertion[.]" *Id.* at *28.

As to the third proposition that the pertussis toxin damages the nervous system, the Special Master faulted Dr. Kinsbourne for changing his reasoning. *Id.* First, he put forward a theory "that pertussis toxin 'uncouples the G protein receptors . . . [that] have inhibitory control over voltage gated sodium channels.'" *Id.* (quoting Pet. Ex. 35 at 11) (alterations in Special Master's Decision). But at the hearing Dr. Kinsbourne asserted "that the SCN1A gene affects

neurons that inhibit seizures and that pertussis's effect on G proteins also affects inhibitory neuron[,]" and thus the two influences converged to affect N.S.'s disorder. *Id.* (citing TR at 33-34). In support of this theory, Kinsbourne discussed articles (later entered into evidence) by CATTERALL (2008) (Pet. Ex. 89) and THALMANN (1988) (Pet. Ex. 94). *Id.* When Dr. Wiznitzer rebutted the notion that the THALMANN article discussed sodium channels, Dr. Kinsbourne denied that he had asserted the article concerned sodium channels and posited "that the Thalmann article showed that G-proteins control inhibitory neurons with a potassium channel[.]"[33] *Id.* (citing TR at 375-76).

The Special Master next looked to the effect of pertussis toxin on neurons by examining a study done by the English government titled the National Childhood Encephalopathy Study ("NCES") (Pet. Ex. 35). *Id.* This study found that there was a greater incidence of acute neurological incidents within a month of receiving the DTP vaccine, *i.e.*, the whole-cell version of the pertussis vaccine. *Id.* The Special Master found using a study about the whole-cell pertussis vaccine to draw conclusions concerning the acelluar pertussis vaccine "problematic," noting that other special masters have rejected similar extrapolations in several cases. *Id.* at *30 (citing *Stone* v. *Sec'y of HHS*, No. 04-1041V, 2010 WL 1848220, at *10 n.15 (Fed. Cl. Spec. Mstr.. Apr. 15, 2010), *remanded on other grounds* 95 Fed. Cl. 233 (2010); *Teller* v. *Sec'y of HHS*, No. 06-804V, 2009 WL 255622, at *4 n.9 (Fed. Cl. Spec. Mstr.. Jan. 13, 2009); *Simon* v. *Sec'y of HHS*, No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1 2007)). The Special Master also found, Dr. Wiznitzer was not better qualified to interpret the NCES study than Dr. Kinsbourne. *Id.* Since the evidence "clearly and convincingly" shows that N.S. would have been the same due to the SCN1A mutation, the Special Master decided he did not need to draw a conclusion about applying studies on whole-cell pertussis vaccine to the acellular pertussis vaccine. *Id.*

As to Petitioners' second theory, *i.e.*, that the pertussis vaccine caused a fever that then caused the seizure that then substantially contributed to the SMEI, the Special Master found that "[a] preponderance of evidence supports finding that DTaP vaccine can cause fevers and fevers can cause seizures." *Id.* The critical issue is then whether the DTaP, even if it caused the first seizure, affected N.S.'s ultimate outcome. *Id.*

The Special Master's discussion then focused on two different mice studies, one discussed in OAKLEY (2009) (Gov't Ex. CC) and one discussed in YU (2006) (Gov't Ex. WW), in which the equivalent of the SCN1A gene had been knocked-out to determine if the mice would develop seizures. *Id.* at *31-32. The dispute over the articles concerned whether the mice were heated before they began to experience spontaneous seizures. Petitioners argued that the mice in the YU article must have experienced elevated temperatures after having surgically implanted electrodes removed. *Id.* at *33 (citing Pet. Resp. at 2). The Special Master found this interpretation "strained" and ultimately unpersuasive, in part because the authors of the YU article "did not report any temperature measurements after surgery." *Id.* Given this finding, the Special Master concluded that the experiments showed that the mice would develop seizures

[33] As the Special Master noted, "[n]eurons contain different types of channels, including sodium channels, potassium channels, and calcium channels." *Id.* at 28 n. 26 (citing TR at 241 (Dr. Wiznitzer); TR at 376 (Dr. Kinsbourne); TR at 562 (Dr. Raymond)).

regardless of whether they had been heated, and thus "[h]umans with [an SCN1A] mutation do not need to have a fever to have a seizure." *Id.* Moreover, the Special Master noted that all human cases of SMEI do not start with fevers, although in many cases the first seizure is associated with a fever. *Id.* In sum, with regard to the Petitioners' fever-based theory, the Special Master found that N.S. "would have had a seizure even if he never had a fever. The seizure was an inevitable result of the SCN1A mutation. The fever did not affect [N.S.'s] development." *Id.* at *34.

The Special Master also addressed Petitioners' related argument that the length of the initial seizure caused additional brain damage. *Id.* The Special Master pointed out that Dr. Kinsbourne only offered testimony on this point. *Id.* In response, Dr. Wiznitzer testified that, although lasting brain damage is possible from an episode like the one N.S. experienced, one would expect to see injury to the brain within a few days of the seizure. *Id.* (citing TR at 257-258). The neuroimaging tests taken after N.S.'s initial seizure did not show any such damage. *Id.* (citing TR at 257-59, 327-28; Pet. Ex. 4 at 323-24 (results of CT scan taken after N.S.'s first seizure)). The Special Master found this testimony more persuasive, and thus concluded that that the Petitioners failed to present any persuasive evidence of lasting neurological damage in N.S.'s case. *Id.*

In addition, the Special Master examined whether Petitioners established that N.S. suffered an injury lasting more than six months, an inquiry the Special Master called an "alternative method for analyzing [N.S.'s] case[.]" *Id.* The Special Master pointed out that Dr. Kinsbourne refused to offer an opinion as to how N.S. would have been different but for the vaccination. *Id.* at *34-35 (citing TR at 118, 580-88). The Special Master found Dr. Kinsbourne's opinion that persons with the defect might suffer a disorder lower on the SMEI spectrum "inherently speculative." *Id.* at *35. In contrast, the Government's experts were certain that the vaccine did not alter N.S.'s outcome. *Id.* (citing TR at 222-23, 226, 346, 349-50 (Dr. Wiznitzer); TR at 446, 474, 523, 546 (Dr. Raymond)). This testimony the Special Master found "compelling." *Id.*

Finally, the Special Master pointed out that no expert asserted that the fever alone caused lasting consequences. *Id.* at *36. Moreover, Dr. Kinsbourne did not say whether the fever was necessary to trigger the seizure disorder. *Id.* (citing TR at 108). In contrast, the Government's experts "were more emphatic" in rejecting the idea that the fever altered the outcome, including the notions that the initial fever would lower the seizure threshold or that the length and type of seizure affected the ultimate outcome. *Id.* (citing TR at 237, 306, 256-57 (Dr. Wiznitzer); TR at 460, 518-19 (Dr. Raymond)).

On this basis, the Special Master found that the DTaP vaccine did not affect N.S.'s SMEI for more than six months and was more consistent with the view that N.S.'s impaired development would have been the same, but for the DTaP vaccine. *Id.* This finding was "derive[d] from the finding that the genetic mutation was the sole cause of [N.S.'s] epilepsy." *Id.*

C. Petitioner Has Established Entitlement To Compensation Under The Vaccine Act.

1. Petitioner Has Demonstrated, By A Preponderance Of The Evidence, That His SMEI Syndrome Was Caused-In-Fact By The DTaP Vaccine.

The United States Court of Appeals for the Federal Circuit held in *Althen* v. *Sec'y of HHS*, 418 F.3d 1274 (Fed. Cir. 2005), that a claim under the Vaccine Act for injury, based on causation-in-fact, requires the petitioner to establish three elements by a preponderance of evidence:

> (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between [the] vaccination and injury.

Id. at 1278; *see also id*. at 1280 (holding that none of these elements are required to be established by "scientific certainty," but only by a preponderance of evidence); *see also Capizzano* v. *Sec'y of HHS*, 440 F.3d 1317, 1324 (Fed. Cir. 2006) (same).

Therefore, to show causation, a petitioner need not show that the vaccine was the *only* cause of his injury, but only that it was a "'substantial factor' in bringing about the harm, and that the harm would not have occurred but for the action." *Shyface* v. *Sec'y of HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999) (quoting RESTATEMENT (SECOND) OF TORTS § 431 (1965)). Evidence proffered to establish one element of the *Althen* test also may establish another element. *See Capizzano*, 440 F.3d at 1326.

In this case, the Special Master assumed or conceded in the Decision Denying Compensation that Petitioners satisfied their burden to establish causation-in-fact under *Althen*, but described this finding as "generous." *See Snyder*, 2011 WL 3022544 at *12. Later in the Decision, however, the Special Master revisited the alternative medical theories posited by Dr. Kinsbourne. *Id*. at **25-34. The Special Master characterized Dr. Kinsbourne's opinion as to "how pertussis toxin affects neurons" as "difficult" to evaluate, because his explanations seemed to change at different junctures during the litigation. *Id*. at **28-29. Nevertheless, the Special Master found "there were shortcomings in the parties' presentations" as to "whether acellular pertussis vaccine can damage brain cells[.]" *Id.* at *30. Accordingly, the Special Master declined to make a conclusion about this theory. *Id*.

Next, the Special Master turned to the medical theory that "the pertussis vaccine substantially contributed to the fever and seizure that substantially contributed to [N.S.'s] SMEI." *Id.* Here, the Special Master found that "[a] preponderance of evidence supports finding that DTaP vaccine can cause fevers and fevers can cause seizures." *Id*. at *30. After a detailed discussion about two medical articles reporting on an experiment on mice resulting in a mixed record and a "divergent understanding of the experiments," the Special Master proceeded to find "[h]umans with a genetic mutation do not need to have a fever to have a seizure." *Id.* at **32-33.

On that basis, the Special Master implicitly rejected Petitioners' pertussis/fever/seizure theory, because it lacked medical scientific certainty. *Id*. at *33; *see also id*. ("[Petitioners] have been given more than one opportunity to address the experiments conducted by the Catterall group of researchers, including the studies reported by Oakley and Yu. [Petitioners] could have submitted evidence in the form of a supplemental report from Dr. Kinsbourne. Yet even after these opportunities, [Petitioners] have not presented any persuasive argument to distinguish these studies."). In doing so, the Special Master applied the wrong standard of proof and erred as a matter of law in determining that Petitioners failed to establish a medical theory causally connecting the vaccine and the injury. *See Knudsen ex rel. Knudsen* v. *Sec'y of HHS*, 35 F.3d 543, 549 (Fed. Cir. 1994) ("'[S]cientific certainty' is not the standard of proof[.]" (quoting *Bunting* v. *Sec'y of HHS*, 931 F.2d 867, 873 (Fed. Cir.1991))).

Petitioners proffered the expert medical opinion of Dr. Kinsbourne that an infant with a SCN1A mutation has a "genetic susceptibility" to SMEI, but an external environmental factor, such as exposure to the acellular pertussis component of the DTaP vaccine, can induce the type of febrile seizures experienced by children who later are diagnosed with SMEI. Pet Ex. 32 at 4-11. This theory is supported by the warning labels of the DTaP vaccine manufacturer advising that, despite detoxification, sufficient pertussis toxin may be present to trigger fever and seizures. Pet. Ex. 98 at 1 (citing Sanofi Pasteur warning labels on Daptacel® (available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf)). For this same reason, Dr. Halthore, a pediatric neurologist, decided on March 7, 2005, two days after N.S.'s first febrile seizure, following a second DTaP injection, to engage in a "long conversation" with N.S.'s parents about the relationship between vaccines and seizures. Pet. Ex. 6 at 20. The record also establishes that after N.S.'s first febrile seizure, others followed on a regular basis resulting in developmental delay. *See e.g.*, Pet. Ex. 26; Pet. Ex. 65 (updated medical records from Neurology Specialists); Pet. Ex. 87 (same). The Special Master, however, found that "[the] evidence convincingly establishes that [N.S.'s] fever did not affect his development. The primary evidence supporting this finding is [the mice experiment, reported in OAKLEY (2009) (Gov't Ex CC)]." *Snyder*, 2011 WL 3022544 at * 31. Again, the Special Master misapplied the standard of proof. *See Andreu* v. *Sec'y of HHS*, 569 F.3d 1367, 1377 (Fed. Cir. 2009) (holding that the special master "erred in requiring . . . conclusive evidence in the medical literature linking . . . the DPT vaccine [to the Petitioners' injury]," because doing so would increase a claimant's burden under the Vaccine Act). Instead, "[m]edical literature and epidemiological evidence must be viewed . . . not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard[.]" *Id.* at 1380.

In addition, the fact that medical literature relied on by Dr. Kinsbourne regarding the necessity of a "gene-gene or environmental interaction" to induce a seizure response was contradicted by other medical literature, suggesting that mosaic parents and "spontaneous mutations in SCN1A" explain why children of asymptomatic parents nevertheless can develop SMEI or another seizure disorder is not dispositive. Gov't Ex. A at 4-8. Again, only a "simple preponderance of evidence" is required, "not scientific certainty." Petitioners are not required to proffer "epidemiologic studies" or "general acceptance in the scientific or medical communities." As the United States Court of Appeals for the Federal Circuit recognized in *Andreu*, 569 F.3d at 1378, medical literature does not attribute causation "until a level of *very near certainty*—perhaps 95% probability—is achieved." *Id*. at 1380 (internal quotation marks

and citations omitted). Under the Vaccine Act, causation-in-fact is determined on a much lower standard, *i.e.*, whether causation is "*logical*" and "*legally probable*." *Id.* at 1380 (internal quotation marks and citations omitted). For these reasons, the court has determined that Petitioners have met their burden to demonstrate that it was more probable than not that the DTaP vaccine was at least a "substantial factor" in bringing about N.S.'s first febrile seizure, followed by a sufficient number of other febrile seizures to be diagnosed as SMEI, with its attendant developmental condition. *See Althen*, 418 F.3d at 1279; *see also Shyface*, 165 F.3d at 1353 (holding that petitioner had demonstrated causation, even where the vaccine "was not the predominant cause" of petitioners' injury).

As to the logical sequence of cause and effect, N.S.'s medical records show that within hours after receiving a DTaP vaccination on March 4, 2005, N.S. experienced the first of over seventy seizures that followed. Pet. Ex. 27 ¶¶ 7-8, 18.

Finally, regarding the proximate temporal relationship, the record evidences that N.S. received a DTaP vaccination on March 4, 2005 followed by "Seizure disorder[.] Acute life[-] threatening event[.] Post vaccination syndrome[.]" Pet. Ex. 4 at 254.[34]

Because the Special Master acknowledged that the Petitioners' evidence on causation could be read to demonstrate causation-in-fact, Petitioners have satisfied their burden to establish, by a preponderance of the evidence, that the DTaP vaccine can be a substantial factor in causing SMEI.

Therefore, the court's review turns to what the Special Master characterized as "the key dispute in this case" — whether the SCN1A mutation "was sufficient by itself," *i.e.*, alone, to cause N.S.'s impaired "development." *Snyder*, 2011 WL 3022544 at *12.

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[34] Because the court has determined that the Petitioners have established causation-in-fact, the court does not need to consider Petitioners' alternative argument that the DTaP vaccine "significantly aggravated" N.S.'s preexisting condition of a SCN1A gene mutation. *See* 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I); *see also* 42 U.S.C. § 300aa-33(4) (defining "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 of health"). In *Whitecotton ex rel. Whitecotton* v. *Sec'y of HHS*, 81 F.3d 1099 (Fed Cir. 1996), the United States Court of Appeals for the Federal Circuit held that in analyzing a significant aggravation claim in the context of a Table injury, a special master must "(1) assess the person's condition prior to administration of the vaccine, (2) assess the person's current condition, and (3) determine if the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination within the meaning of the statute." *Id*. at 1107. The United States Court of Appeals for the Federal Circuit, however, has not yet considered a non-table case alleging "significant aggravation" causation.

This issue has been addressed, however, by the United States Court of Federal Claims in *Loving* v. *Sec'y of HHS*, 86 Fed. Cl. 135 (2009), wherein it was determined that the proper test was to combine the *Whitecotton* significant aggravation test with the elements identified in *Althen*. *Id*. at 144. *Loving* is on remand to the special master. Our appellate court should first have the opportunity to determine whether that analysis should be afforded precedential status.

2. The Special Master Erred In Finding That The Government Demonstrated Alternate Causation.

The text of the Vaccine Act presents the dispositive issue on alternative causation as whether a petitioner has established "that there is not a preponderance of the evidence that the illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition." 42 U.S.C. § 300aa-13(a)(1)(B).

There is no evidence in this record, scientific or otherwise, that establishes that a child with a SCN1A mutation, *necessarily* will develop SMEI or another seizure disorder. The Special Master's finding that Petitioners did not "present[] persuasive evidence" in support of their theory "that an environmental trigger is necessary to cause symptoms" answers the wrong question. *Snyder*, 2011 WL 3022544 at *21**.** In the causation-in-fact analysis a petitioner need only show a connection between the vaccine and the disease in question. Having done so, the burden shifts to the Government to demonstrate alternate causation.

What the record establishes is that N.S. was born with a SCN1A gene mutation (Pet. Ex. 13 at 4), but was healthy and did not experience any seizures during the first four months of his life, until he received a second DTaP shot. Pet. Ex. 27 ¶¶ 5-6. The record also establishes that a vaccination with acellular pertussis can cause a fever. Pet. Ex. 98 at 2 (citing Sanofi Pasteur warning labels on Daptacel® (available at http://www.fda.gov/downloads/Biologics BloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf)). On March 4, 2005, the day that N.S. received a second DTaP shot, he developed a febrile seizure. Pet. Ex. 27 ¶¶ 5-8. The record also evidences that SMEI manifests itself during the first year of life with febrile seizures. Pet Ex. 46 at 844. The fact that N.S.'s parents did not develop or display a seizure disorder strongly indicates that some other factor or factors, whether it be genetic, *i.e.*, *de novo* mutation, or environmental, as Dr. Kinsbourne suggests, was required to induce N.S.'s seizures. In addition, Dr. Raymond opined that "[w]hether a particular mutation is severe or not is based on several lines of evidence" and that mutations like N.S.'s "ha[ve] been previously reported to result in SMEI." Gov't Ex. C at 4, 5. He never, however, suggested that a child with an SCN1A mutation necessarily will develop or manifest SMEI.

In conducting the § 300aa-13(a)(1)(B) analysis, the United States Court of Appeals for the Federal Circuit has held that the Government is "required not only to prove the existence of [a preexisting condition], but *also* to prove by a preponderance of the evidence that the particular [preexisting condition] present in the child actually *caused* the . . . injury complained of." *See Knudsen*, 35 F.3d at 549. The Government's burden to prove alternate causation is a heavy one; once a petitioner demonstrates causation-in-fact, the Government can prevail only if it demonstrates, by a preponderance of the evidence, that a proposed alternative cause was the "*sole* substantial factor in bringing about the injury." *De Bazan* v. *Sec'y of HHS*, 539 F.3d 1347, 1354 (Fed. Cir. 2008). Otherwise "a child could never recover under the Vaccine Act if the [G]overnment demonstrated that the child had a [preexisting condition] at the time of vaccination or injury." *Knudsen*, 35 F.3d at 549-50; *see also Althen*, 418 F.3d at 1282. But, that is what happened in this case. The Special Master properly concluded that the *existence* of SCN1A

mutation can be an alternative cause, but erred in finding that the SCN1A mutation "*was* in fact an alternative caus[e]." *Knudsen*, 35 F.3d. at 550.

Much of the conflict among the parties' experts and the primary focus of the Decision Denying Entitlement, (*Snyder*, 2011 WL 3022544 at *16-21, 23, 23-33), concerned the interpretation and significance of 31 medical articles on a variety of relevant issues. Mutations in the SCN1A and SCN1B genes that encode the protein components of the brain sodium ion channel $Na_v1.1$ were not discovered until 1999 and 2000. Therefore, it comes as no surprise that the influence of these gene mutations on SMEI and other seizure disorders continues to be debated in the academic medical community. Although 70-80% of children with SMEI have SCN1A mutations, that does not necessarily mean that the majority of SMEI cases are caused by SCN1A mutations, and it certainly does not mean that an SCN1A mutation is the "*sole substantial*" cause of each case of SMEI. *See* Pet. Ex. 99 at 1 (discussing MCINTOSH (2010) (Gov't Ex. VV)). In other words, although there is a relationship between SCN1A gene mutations and SMEI, a one-to-one relationship has not been established, nor has it been determined that exposing a patient with a SCN1A mutation to acellular pertussis will have no adverse consequences. *See* MCINTOSH (2010) (Gov't Ex. VV) at 6 ("Our study design and absence of a control group of patients with [SMEI] who did not have DTP vaccinations precluded us from examining a gene-environment interaction."). All of this academic medical debate and the Special Master's interpretation thereof ignores a central tenant of *Althen* that "requiring medical literature . . . contravenes section 300aa-13(a)(1)'s allowance of medical opinion as proof." *Althen*, 418 F.3d at 1280. As the United States Court of Appeals for the Federal Circuit explained in that case, requiring a medical theory to be endorsed or supported by medical literature "prevents the use of circumstantial evidence envisioned by the preponderance standard and negates the system created by Congress in which close calls regarding causation are [to be] resolved in favor of injured claimants." *Id*. at 1280 (citing *Knudsen*, 35 F.3d at 549 (explaining "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine program")).

The Special Master determined that Dr. Raymond's testimony was more reliable than Dr. Kinsbourne's, in part because Dr. Raymond was a geneticist. *See Snyder*, 2011 WL 3022544 at **16, 22. But the Special Master did not mention Dr. Kinsbourne's explanation that, because of his extensive training and experience as a pediatric neurologist, he had substantial academic and other training in gene-related disorders, as did Dr. Wiznitzer. Pet. Ex. 80 at 2; *see also Moberly ex. rel. Moberly* v. *Sec'y of HHS*, 592 F.3d 1315, 1326 (2010) ("Finders of fact 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 persons presenting that evidence. *What Andreu prohibited was for the finder of fact to reject evidence based on an unduly stringent legal test while characterizing the rejection as based on the reliability of particular evidence or the credibility of a particular witness.*" (emphasis added)); *see also Porter*, 2011 WL 5840315.[35]

[35] The court has carefully reviewed the written and oral testimony of Dr. Kinsbourne and found that his analysis and insights were helpful and instructive, as were those of the Government's experts, Dr. Wiznitzer and Dr. Raymond. The court was impressed by the fact

that all of the experts proffered by the parties had outstanding and relevant professional credentials. The Special Master, however, found that

> Dr. Kinsbourne expressed opinions that are outside of his field of expertise, such as the toxoiding process. Within Dr. Kinsbourne's *ostensible* field of expertise, pediatric neurology, he was much less knowledgeable than Dr. Wiznitzer, who continues to practice pediatric neurology.

Snyder, 2011 WL 3022544 at *37 (emphasis added).

Dr. Kinsbourne's unchallenged reference to written warnings of the manufacturer of the DTaP vaccine was not an "opinion" about the "toxoiding process;" rather, he simply was repeating the manufacturer's superior knowledge about those products. In addition, and more important, the Special Master's condescending mischaracterization of Dr. Kinsbourne's *bona fides* is out of line. Dr. Kinsbourne is not "ostensibly" a pediatric neurologist. *See id.* at *37. No lesser academic institutions than Oxford University, Duke University Medical Center, the University of Toronto, Harvard Medical School, Boston University, and Tufts University have recognized Dr. Kinsbourne as an expert in this field, contrary to the views of the Special Master. Pet. Ex. 33 at 1-2. The Special Master also misrepresented Dr. Kinsbourne's current position in the New School in New York City, where he teaches neuroscience, not psychology, as the Special Master implies. *Compare id*. at 2 *with Snyder*, 2011 WL 3022544 at *5. Finally, the Special Master emphasized that Dr. Kinsbourne is "well-known" to special masters, because he testifies frequently in the Vaccine Program for petitioners. *See Snyder*, 2011 WL 3022544 at *5. Of course, the Special Master made no mention of the fact that the same is true of Dr. Wiznitzer. The Special Master's proclivity to demean petitioners and their experts when he differs with their opinions is not required to make a credibility determination. *See e.g.*, *Porter*, 2011 WL 5840315 at **13-15 & n.4 (Fed. Cir. Nov. 22, 2011) (O'Malley, J. dissenting) (discussing this Special Master's "remarkable" opinion for "the sheer number of references to credibility, demeanor and veracity" and character attack on an expert with whom he disagreed); *Dobrydneva* v. *Sec. of HHS*, 94 Fed. Cl. 134, 147 (2010) (noting the Special Master's "near obsession with discrediting [Petitioner's] mother's contemporary observations[.]"); *Campbell* v. *Sec'y of HHS*, 90 Fed. Cl. 369, 383-84 (2009) (the Special Masters' misevaluation of an expert's credibility "pervaded this analysis"). The modest hourly compensation that physicians receive for rendering a professional medical opinion, based on decades of experience, does not compensate them for *argumentum ad hominem* disguised as "credibility determinations." Professional careers of physicians are built and maintained based on their reputation in the medical community and among their peers. What rational, established physician would want to risk an assault on his credentials and professional standing to render an opinion in a Vaccine Act case under these circumstances? The undersigned judge has seen other cases where knowledgeable physicians have declined to render a relevant, if not dispositive opinion, because they did not want to be subject to such "credibility determinations." *See* Record in *John Doe 21* v. *Sec'y of HHS*, Docket No. 02-0411V (Dr. Lydia Eviatar, M.D. Professor of Pediatric Neurology at the Long Island Campus of the Albert Einstein College of Medicine declining to testify in remand proceeding before the same Special Master). Allowing this unnecessary and unprofessional conduct to continue has had significant adverse consequences on the Vaccine Act Program.

Moreover, as the United States Court of Appeals for the Federal Circuit stated in *Andreu*, the job of the fact finder is to "make[] a credibility determination . . . not to evaluate whether an expert witness' medical theory is supported by the weight of epidemiological evidence." 569 F.3d at 1379. Of course, that is what happened here. *See Snyder*, 2011 WL 3022544 at **16-23, 26-34.

Therefore, the court views the entirety of the record on alternative causation as a classic case of "conflicting" experts, a situation that the United States Court of Appeals for the Federal Circuit has stated "does not[,] in our view[,] either compel a finding of . . . alternative causation nor preclude one." *Knudsen*, 35 F.3d at 550. When a special master is confronted with such a record, the instruction of our appellate court to the special master is clear:

> If the evidence is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded. . . . especially in view of . . . the "generosity" of the Vaccine Act.

Id. at 550-51.

The Special Master did not follow this directive. Accordingly, his finding that N.S.'s "epilepsy was caused by the genetic mutation" is erroneous as a matter of law, because the Government failed to meet its burden of proof to establish that the presence of a SCN1A mutation was not merely a possible alternate cause of N.S.'s first febrile seizure and SMEI, but was, in fact, the sole cause, of N.S.'s first febrile seizure and subsequent SMEI.[36]

IV. CONCLUSION.

For these reasons, the court has determined that the record has established that Petitioners' Motion For Review is granted. The Special Master's Decision is reversed. This case is remanded to the Special Master for an award of compensation to the Petitioners, reasonable attorney fees, and other costs.

IT IS SO ORDERED.

s/ Susan G. Braden
SUSAN G. BRADEN
Judge

[36] To the extent that the Special Master made a factual determination that the Government carried its heavy burden of proof, it was arbitrary and capricious because the Special Master afforded too much weight to the Government's evidence that SMEI *can*, in theory, arise absent a vaccine or a vaccine-induced fever. *See Knudsen*, 35 F.3d at 548 ("Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules.").