IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

FRANK HARRIS, parent of	*	No. 07-60V
JORDAN HARRIS, a minor,	*	Special Master Christian J. Moran
	*	
Petitioner,	*	Filed: May 27, 2011
	*	
v.	*	entitlement, DTaP, epilepsy, seizure
	*	disorder, SMEI, GEFS+, genetic
	*	mutation, SCN1A, acellular pertussis
SECRETARY OF HEALTH	*	vaccine compared to whole-cell
AND HUMAN SERVICES,	*	pertussis vaccine, NCES, six-month
	*	requirement
Respondent.	*	

Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA., for petitioner;
Voris E. Johnson, United States Dep't of Justice, Washington, D.C. for respondent.

DECISION DENYING COMPENSATION*

* Because this published decision contains a reasoned explanation for the special master's action in this case, the special master intends to post it on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision is filed, a party has 14 days to identify and to move to delete such information before the document's disclosure. If the special master, upon review, agrees that the identified material fits within the categories listed above, the special master shall delete such material from public access. 42 U.S.C. § 300aa–12(d)(4); Vaccine Rule 18(b).

Jordan Harris has a mutation in a gene, known as the SCN1A gene that is associated with various types of epilepsy including Dravet's syndrome, severe myoclonic epilepsy of infancy (SMEI), or generalized epilepsy with febrile seizures plus (GEFS+). Jordan has GEFS+. The first manifestation of Jordan's epilepsy was a seizure that occurred within 12 hours of Jordan's receiving a dose of the diphtheria-tetanus-acellular pertussis ("DTaP") vaccine in 2004. Jordan's father, Frank Harris, claims that the acellular pertussis component of this vaccine made Jordan's epilepsy worse than it would have been but for the vaccine. Mr. Harris seeks compensation pursuant to the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa—10 et seq. (2006). Respondent counters that the mutation in the SCN1A gene caused Jordan's condition and the acellular pertussis vaccine did not affect Jordan's development at all.

Thus, Mr. Harris's case presents two distinct topics. The first is whether the acellular form of the pertussis vaccine can cause a neurological injury. Mr. Harris and his expert, Dr. Kinsbourne, make several assertions that were challenged by respondent and her expert, Dr. Wiznitzer. Although the evidence for and against these assertions is discussed, ultimately, whether DTaP can cause a significant neurological injury is not determined. Resolution is not necessary because even if Mr. Harris were assumed to have met his burden of proof on these questions, Mr. Harris would still not be entitled to compensation because of the evidence regarding the second topic.

The other topic is the degree to which Jordan's genetic mutation caused his epilepsy. The evidence convincingly shows that the genetic mutation is the sole cause of Jordan's epilepsy. Evidence introduced by respondent was much stronger than the evidence introduced by Mr. Harris. The simplest demonstration of the disparity in evidence is that respondent supplied the testimony of a practicing geneticist, Dr. Raymond. In contrast, Mr. Harris relies upon the testimony of Dr. Kinsbourne, someone who has no special training in genetics and who stopped practicing pediatric neurology in 1981. Dr. Raymond's testimony that the genetic mutation was the sole cause of Jordan's epilepsy constitutes a persuasive reason for finding that the DTaP vaccine did not affect Jordan's development.

In short, the weight of the evidence shows that Mr. Harris is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

I. Factual Background

In this case, the parties do not dispute the factual context for Mr. Harris's claim that a vaccine adversely affected Jordan's health and respondent's argument that genetics alone determined Jordan's development. The meaningful factual context for evaluating the parties' competing claims includes what is known about genetics generally and what happened to Jordan specifically. These two different subjects are discussed in the following sections.

A. Jordan's Medical History

Jordan was born in March 2004, after an uneventful pregnancy and delivery. Exhibit 2 at 3; exhibit 12 ¶ 2. He appeared to be a healthy baby at his early well-baby visits. Exhibit 4 at 137-38.

At his two-month appointment, Jordan also appeared normal. He received several vaccines, including the DTaP vaccine. Exhibit 5 at 2. Several hours after these vaccinations, Jordan stared at the ceiling, and made grunting noises. Exhibit 4 at 22 (record from emergency room); exhibit 12 (mother's affidavit). Jordan was taken to an emergency room and was noted to have a temperature of 101.1° F. Jordan was diagnosed as having a fever and a seizure. Exhibit 4 at 17. Later, the admitting doctor indicated that Jordan may have had a seizure episode versus a vaccine reaction. Id. at 29. Jordan was discharged two days later.

At his four-month well-baby appointment, Jordan received another set of vaccinations, including another dose of DTaP. He received a third dose of DTaP as part of the six-month appointment on September 3, 2004. Exhibit 5 at 2.

On September 28, 2004, when Jordan was six months old, he had a second seizure. Jordan was admitted to a hospital, where he was checked by a neurologist. A magnetic resonance imaging ("MRI") and an electroencephalogram ("EEG") were normal. Exhibit 7 at 44-47.

Periodically Jordan had additional seizures for which he was treated by various doctors. Eventually, in August 2006, Jordan was referred for genetic testing. Athena Diagnostics, Inc. identified two DNA variants in Jordan. Exhibit 6 at 51-54. One of the mutations was eventually determined to be inherited from Jordan's father and is not known to be a marker for disease. Tr. 152; tr. 449. The other mutation was a "variant in the SCN1A gene that is predicted to be a disease-

associated mutation." This variant was "predicted to disrupt the structure of the protein and alter its function." The report from Athena continued: "this test result is consistent with a diagnosis of, or a predisposition to developing, SMEI or SMEB, the severe phenotype associated with SCN1A mutations." Exhibit 6 at 51. (SCN1A, SMEI, and SMEB are discussed in the following section.)

Jordan's seizures were controlled with medications. His recent neurologic examinations have been normal. Exhibit 58 at 1-4.

B. SCN1A and Sodium Channels

SCN1A is a gene that codes a sodium channel. This sodium channel, which is sometimes referred to as $Na_v1.1$, is a voltage-gated sodium channel, meaning that passage is either open or closed. Tr. 54 (Dr. Kinsbourne); tr. 296 (Dr. Wiznitzer); tr. 434-36 (Dr. Raymond).

The purpose of the sodium channel is to regulate the flow of sodium ions (charged particles) from one neuron to the next. Tr. 32; Mulley.[1] A proper flowing of sodium ions through this channel allows neurons with this sodium channel to fire properly. Ceulemans (2004a) at 237.

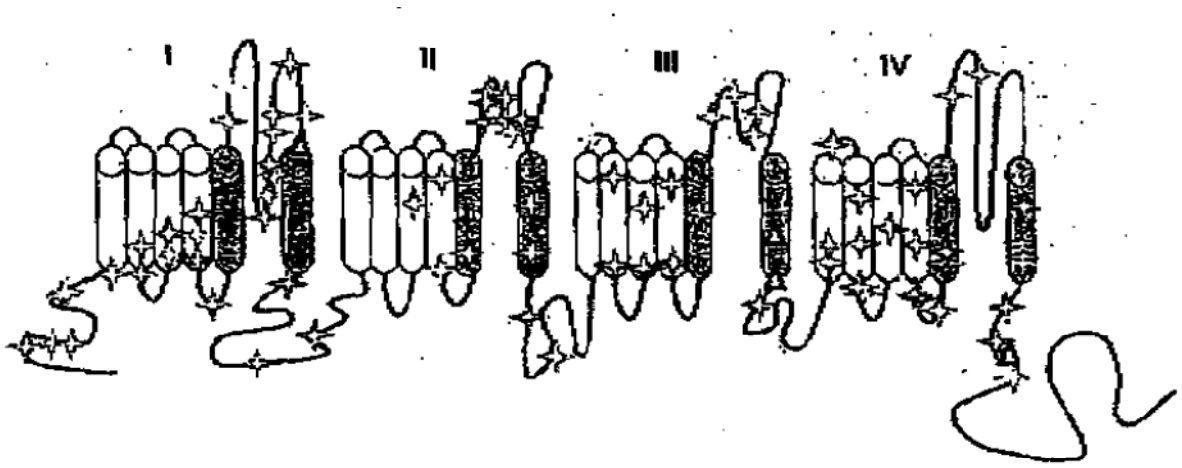
Abnormal function of the sodium channel may cause a person to have seizures. Seizures arise when neurons that excite electrical impulses are not balanced by neurons that inhibit electrical impulses. An imbalance results from either too many exciting neurons or too few inhibitory neurons. Tr. 29 (Dr. Kinsbourne); tr. 33 (same); tr. 302 (Dr. Wiznitzer); tr. 364 (Dr. Kinsbourne); tr. 572 (Dr. Kinsbourne); see also Turnbull at 2492. An imbalance appears to be one step in the process of generating seizures but all imbalances do not lead to seizures. Tr. 313-15 (Dr Wiznitzer); tr. 515-16 (Dr. Raymond).

Defects in the $Na_v1.1$ sodium channel foster seizures because, according to Dr. Kinsbourne, the sodium channel is located in a neuron that inhibits electrical impulses. When the sodium channel is defective, the neuron does not inhibit electrical impulses effectively, so that there is an overabundance of excitation and

[1] This decision references medical articles by the last name of the first author. A complete citation to each article appears in the appendix.

seizures result. Tr. 33; see also tr. 118; but see Turnbull at 2492 (categorizing a sodium channel as an "excitatory ion channel.").

The sodium channel contains approximately 2,000 amino acids. Lossin at 3. A depiction of it is:



Depienne, figure 2.

More than 600 different mutations in the SCN1A gene have been identified. Tr. 83. These mutations are associated with (or cause) a variety of problems. Depending on the range of symptoms and the severity of symptoms a person could be classified as suffering from familial hemiplegic migraines, generalized epilepsy with febrile seizures plus ("GEFS+"), or severe myoclonic epilepsy of infancy ("SMEI"). In this case, Jordan suffers from a severe form of GEFS+. Tr. 86 (Dr. Kinsbourne); tr. 211 (Dr. Wiznitzer).

SMEI typically is first manifested as a seizure that occurs when the child is between six and nine months. The first seizure usually happens in the context of a fever. The early seizures are usually myoclonic, meaning there are sudden muscle jerks. Tr. 60. Later seizures are more often tonic-clonic seizures. Although the child's early development is normal, mental development stagnates in the second year of life and children are frequently mentally retarded. Ceulemans (2004a) at 236.

GEFS+ is a disorder that is considered sufficiently similar to SMEI that they are sometimes described as falling on one spectrum. Tr. 63 (Dr. Kinsbourne);

tr. 198-99 (Dr. Wiznitzer); Turnbull at 2493. GEFS+ is milder than SMEI and GEFS+ occurs more frequently than SMEI. Tr. 61-64; tr. 200-01.[2] Unlike SMEI, people with GEFS+ do not always have a recognized mutation in the SCN1A gene. Mutations in the SCN1A gene are found in only approximately 5 to 10 percent of GEFS+ cases. Tr. 61 (Dr. Kinsbourne) . The prognosis for people with GEFS+ is "good." Ceulemans (2004a) at 237.

II. Procedural History

Mr. Harris filed this petition on January 24, 2007, and the first set of medical records in May 2007. In an amended petition, which was filed on July 12, 2007, Mr. Harris alleged that "[a]s a result of receiving a DTaP vaccine on May 7, 2004, Jordan suffered the onset of a seizure disorder." Amended Pet., preliminary paragraph. Mr. Harris also maintained that "it is entirely possible for [an] SCN1A mutation to have remained dormant in Jordan absent a causal agent, such as the vaccine." Id. ¶ 38.

Respondent filed her report and recommended that compensation be denied. Respondent maintained that "the but-for cause of Jordan's seizure disorder is his underlying genetic condition." Resp't Rep't, filed August 20, 2007, at 6. For this assertion, respondent relied upon the statements of Dr. Wallerstein (exhibit 6 at 18) and an article by Samuel F. Berkovic and Ingrid Scheffer (among others). As discussed below, the Berkovic article suggested that children with brain damage who were considered to have reacted adversely to a pertussis vaccine actually had their problems caused by a genetic mutation. Respondent also noted that Mr. Harris failed to present a medical opinion to support his claim. Resp't Rep't at 7.

In addition, respondent presented an entirely different reason for denying compensation. According to respondent, Mr. Harris had failed to present evidence that Jordan was affected for more than six months. Instead, according to respondent, there is "no evidence in the medical records that Jordan's genetically-based seizure disorder was made worse as the result of his DTaP vaccination." Id. at 8.

[2] Some articles also refer to an entity falling on the borderline between SMEI and GEFS+, known as SMEB. E.g. Claes (B) at E906; see also tr. 197.

Approximately six months after respondent's report was filed, Mr. Harris presented the report of Dr. Marcel Kinsbourne. Dr. Kinsbourne is well-known to special masters because he testifies frequently in the Vaccine Program. Testifying for petitioners supplied approximately 60 percent of Dr. Kinsbourne's annual income for the last five years. Tr. 97-98; tr. 159-60. Another source of income for Dr. Kinsbourne is compensation for working as a professor in the psychology department of the New School University. Tr. 11-12. His duties as a professor take more time than his work as an expert witness. Tr. 160. As a professor, he teaches mostly graduate students about neuroscience. Tr. 11-13. Some of his students research people's behavior. Tr. 156. His students nominated him for an award for excellence in teaching that the New School University bestowed on Dr. Kinsbourne in 2008. Tr. 12. Dr. Kinsbourne chairs the university's committee overseeing experiments to ensure that the experiments comply with ethical guidelines for treatment of human subjects. Tr. 12-13; tr. 159.

Before starting at New School University in 1994, Dr. Kinsbourne taught at a variety of universities in Massachusetts. He researched developmental disabilities. This work built upon his experience as the director of the behavorial neurology department at the Eunice Kennedy Shriver Center from 1981-91. During this time, Dr. Kinsbourne had a limited private practice as a neurologist. Tr. 10-11; exhibit 22 (curriculum vitae) at 3.

Dr. Kinsbourne worked in the field of neurology with a specialty in pediatric neurology for decades until 1981. He graduated from Oxford University in England in 1952 and had training in pediatric neurology in the 1950s and 1960s. He described a condition called opsoclonus-myoclonus syndrome, which is also known as Kinsbourne syndrome. He has continued to follow developments in the syndrome named for him. Tr. 14-15.

Dr. Kinsbourne's knowledge about pediatric neurology took him from Oxford, England to Duke University in Durham, North Carolina, and to University of Toronto in Ontario, Canada. Tr. 10-11; exhibit 22 at 2-3. When he left the University of Toronto for the Eunice Kennedy Shriver Center in 1981, his practice in pediatric neurology essentially stopped. Tr. 102. In his entire career, Dr. Kinsbourne has not focused on genetics or seizure disorders. The basis of Dr. Kinsbourne's opinions comes from his interpretation of medical articles about genetic epilepsies. This research was done for the purpose of presenting an opinion in this case. Tr. 104.

Dr. Kinsbourne's opinion is that "the DTaP vaccination, which Jordan Harris received on May 7, 2004, made a significant contribution to the causation of his seizure disorder." Exhibit 21 (report) at 10. This conclusion reflects several subsidiary opinions, including an opinion that a "mutation [in the SCN1A gene] alone appears not to be sufficient to account for the associated epilepsy," id. at 5, and that the DTaP vaccine can affect neurological development, id. at 6-8. The bases for these two points are discussed extensively below.

After the filing of Dr. Kinsbourne's report, respondent presented the reports of Dr. Max Wiznitzer and Dr. Gerald V. Raymond. . Dr. Wiznitzer has an active clinical practice in pediatric neurology in which he sees patients in half-day sessions five times per week. He serves as a general neurologist at a hospital where he works as the admitting neurologist on a rotating and periodic basis. He also works in the epilepsy monitoring unit where one of his duties is to interpret electroencephalograms (EEGs). In this capacity, Dr. Wiznitzer has a small amount of administrative responsibilities. Dr. Wiznitzer also teaches medical students about child neurology and conducts research into different topics, including the effectiveness of medications for epilepsy. Tr. 183-87; exhibit D (curriculum vitae) at 3.

Dr. Wiznitzer's training as a pediatric neurologist began in the medical school of Northwestern University from whence he graduated in 1977. He received specialized training in pediatrics and in child neurology from 1977 to 1986 at various institutions. He is board-certified in neurology with a special competence in child neurology and board-certified in neurodevelopment. He is a member of various professional organizations and has positions of responsibility in groups that focus on neurodevelopment and disabilities. Tr. 180-83.

Dr. Wiznitzer has been interested in Dravet's syndrome since the 1980s. He has treated six to eight children with that condition. His interest in Dravet's syndrome led him to participate in the first international conference devoted to Dravet's syndrome, which was held in Verona, Italy, just days before he testified at the hearing in this case. Tr. 186-89. At this conference, he heard a presentation about research on vaccinations conducted by Edward Scheffer. Tr. 329-31.

Respondent's other expert is Dr. Raymond. He is currently an associate professor of neurology at Johns Hopkins University and the director of

neurogenetic research at the Kennedy Krieger Institute. He spends approximately 75 percent of his time on research and his research focuses on a disorder known as adrenoleukodystrophy. Tr. 392-93; tr. 480; exhibit F (curriculum vitae) at 1. Dr. Raymond spends some time teaching medical students and residents about neurology and genetics. Tr. 393. Approximately 15-20 percent of Dr. Raymond's time is spent in clinical practice. Tr. 476. Among his patients, approximately half suffer from epilepsy, including two or three people who have been diagnosed as having Dravet's syndrome. Tr. 476-77; see also tr. 396.

Dr. Raymond graduated from the medical school at the University of Connecticut. He had internships, residencies, and fellowships in pediatrics, neurology and genetics. He has been board-certified in neurology and clinical genetics. According to Dr. Raymond, only four or five people in this country hold board certifications in both neurology and genetics. In treating patients, Dr. Raymond brings his knowledge of neurology to genetic problems and his knowledge of genetics to neurologic problems. He reviews submitted manuscripts before publication in journals focusing on genetics and/or neurology. He belongs to various professional organizations including one, the Teratology Society, that focuses on birth defects. Tr. 392-98; exhibit F at 1-2.

Dr. Wiznitzer and Dr. Raymond disagreed with Dr. Kinsbourne's ultimate conclusion. Dr. Wiznitzer stated that Jordan's condition "is explained by the associated SCN1A gene mutation and its effects on its pore channel product and does not require any 'gene-environment interaction' for causation." Exhibit C at 2. Dr. Raymond concluded that Jordan "has severe, generalized and partial epilepsy secondary to a mutation in his SCN1A gene. This is the sole cause of his epilepsy condition. It was not caused nor exacerbated by any of the immunizations that he received." Exhibit E at 8.

On June 24, 2008, Mr. Harris filed a motion to consolidate this case with Snyder v. Sec'y of Health & Human Servs., No. 07-60. Like Mr. Harris, Mr. and Ms. Snyder alleged that a DTaP vaccine caused their child to develop a seizure disorder. The petitioners in both cases relied upon the opinion of Dr. Kinsbourne. In both cases, respondent maintained that a mutation in the SCN1A gene was solely responsible for the seizure disorder and relied upon the opinions of Dr. Wiznitzer and Dr. Raymond. Finally, the attorneys for both parties were the same. Consequently, the motion to transfer Snyder was granted and Snyder was reassigned to the undersigned.

With the filing of expert reports from both sides, status conferences were held to discuss the next steps for the two cases. During a status conference held on July 23, 2008, Mr. Harris represented that he was attempting to retain a geneticist. The undersigned encouraged Mr. Harris to present a person with expertise in genetics because respondent had already filed the report of Dr. Raymond. See Vaccine Rule 5. On August 11, 2008, a hearing was set for January 29-30, 2009, in Boston, Massachusetts.

This hearing did not proceed as scheduled. On January 13, 2009, approximately two weeks before the hearing's start, Mr. Harris filed a motion to continue the hearing. Mr. Harris requested a finding that his case was supported by a reasonable basis. The reason for Mr. Harris's concern was that on December 19, 2008, respondent sent a letter, stating that Mr. Harris's case lacked a reasonable basis for proceeding to a hearing because Mr. Harris could not rebut the opinion of Dr. Raymond regarding the genetic cause of Jordan's seizure. Alternatively, Mr. Harris requested that his case be deferred until rulings were made in other cases that also presented the SCN1A issue.

After a status conference, Mr. Harris's motion to postpone the hearing was granted. Mr. Harris was permitted an opportunity to present a report from Dr. Kinsbourne, in which Dr. Kinsbourne could address the points made by Dr. Raymond. Mr. Harris did file a report from Dr. Kinsbourne on March 18, 2009. Exhibit 53.

This supplemental report prompted respondent to seek additional reports from Dr. Wiznitzer and Dr. Raymond. These reports were filed on April 24, 2009. Exhibit GG (Dr. Raymond); exhibit TT (Dr. Wiznitzer).

To receive testimony from Dr. Kinsbourne, Dr. Wiznitzer, and Dr. Raymond, a hearing was held in Boston, Massachusetts on October 8-9, 2009. During the hearing, the experts referred to medical articles that had not been filed as exhibits before the hearing. Thus, the parties were ordered to file additional materials after the hearing, including charts listing articles with the exhibit designation (either number or letter) for both Harris and Snyder. Order, filed

October 15, 2009.[3] Each party also presented additional reports from experts discussing articles that had not been filed previously.

In this period after the hearing, respondent requested an opportunity to file a medical article that had not been filed previously because the article had been published only recently. Mr. Harris opposed this motion. The motion was granted because it was impossible for respondent to have presented the article earlier. Mr. Harris was permitted opportunity to present another supplemental report from Dr. Kinsbourne.

Both parties filed initial briefs on May 24, 2010. The parties filed reply briefs on July 19, 2010. Mr. Harris also filed the supplemental report from Dr. Kinsbourne (exhibit 74) on the same date.

Mr. Harris's reply brief contained assertions about a particular experiment done by a group of researchers led by Dr. Catterall. Pet'r Reply at 16. As discussed below, the Catterall experiments are very important to understanding the SCN1A gene and how environmental influences affect – or do not affect – the SCN1A gene. Consequently, additional information from the parties and their experts was sought. Order, filed September 22, 2010. Respondent complied with this order. Mr. Harris, although given an opportunity to explain the basis for the assertion in his reply, did not do so. Thus, a separate order was issued, giving Mr. Harris a second chance. Mr. Harris did make this submission on December 17, 2010. With this submission, the case is ready for adjudication.

III. Standards for Adjudication

There are at least three distinct parts to evaluating whether a petitioner is entitled to compensation. One part is to articulate the elements of the petitioner's case. These elements are "what" petitioner must establish. A separate part of the analysis is the quantum of evidence that a petitioner must introduce, which is the burden of proof. A final aspect is the process of weighing or evaluating the evidence that is submitted. These three portions are discussed separately.

[3] As a result of this process, every article that was filed in Harris was also filed in Snyder and vice-versa. Citations to articles appear in the appendix.

A. Elements of Petitioner's Case

The Vaccine Act sets out five elements for entitlement to compensation, listed in paragraphs (A) through (E) of section 13(a)(1). See also 42 U.S.C. § 300aa-11(c)(1). This case raises issues relating to two parts: paragraph (C), which concerns causation and significant aggravation, and paragraph (D), which concerns the severity of an injury. The ways that petitioners can establish that a vaccine was the cause of an initial injury or that the vaccine significantly aggravated a pre-existing condition are discussed in section IV below. Similarly, a detailed discussion about the severity of the injury is deferred until section V below.

B. Burden of Proof

For the elements that petitioners are required to prove, their burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa−13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty). In this regard, "close calls regarding causation are resolved in favor of injured claimants." Althen, 418 F.3d at 1280.

C. How to Weigh Evidence

The preceding sections explain what a petitioner is required to establish and what level of proof satisfies the petitioner's obligation. The remaining issue is how to evaluate evidence submitted to meet the standard of proof on those elements. Three authorities generally instruct special masters in how to evaluate evidence.

They are Congress, the United States Court of Federal Claims, and the United States Court of Appeals for the Federal Circuit.

Congress is the first authority for instructions about how to weigh evidence. In enacting the National Vaccine Injury Compensation Act, specifically section 13, Congress provided some instructions about how special masters should analyze the evidence. Among other provisions, section 13 dictates that the special master should consider "the record as a whole." Section 13 also provides that the special master shall consider "any diagnosis, conclusion, medical judgment or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition or death." Nevertheless, "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court."

The second authority is the United States Court of Federal Claims. Congress authorized the Court of Federal Claims to promulgate rules of procedure for cases in the Vaccine Program. 42 U.S.C. § 300aa−12(d)(2). Collectively, the judges of the Court of Federal Claims have issued the Vaccine Rules. The Vaccine Rules, in turn, provide that the special master "must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties." Vaccine Rule 8(b)(1). This rule "necessarily contemplates an inquiry into the soundness of scientific evidence to be considered by special masters." Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010).

The third authority is the United States Court of Appeals for the Federal Circuit. Decisions by the Federal Circuit are binding precedent. 42 U.S.C. § 300aa−12(e). Within the Vaccine Program, the Federal Circuit expected that special masters would "consider[] the relevant evidence of record, draw[] plausible inferences and articulate[] a rational basis for the decision." Hines v. Sec'y of Health & Human Servs., 940 F.2d 1518, 1528 (Fed. Cir. 1991).

A particular topic on which the Federal Circuit has guided special masters is the process for evaluating the testimony of expert witnesses. In the Vaccine Program, an expert's opinion may be evaluated according to the factors identified by the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999). As recognized in Terran, the Daubert factors for analyzing the reliability of testimony are:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2, citing Daubert, 509 U.S. at 592-95.

After Terran, decisions from judges of the Court of Federal Claims have consistently cited to Daubert. E.g. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 742-45 (2009); Cedillo v. Sec'y of Health & Human Servs., 89 Fed. Cl. 158, 182 (2009), aff'd, 617 F.3d 1328, 1347 (Fed. Cir. 2010); De Bazan v. Sec'y of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) ("A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness's testimony regarding causation."), rev'd on other grounds, 539 F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec'y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

The reliability of the expert's theory is not presumed. A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324. Furthermore, the reliability of an expert's theory affects the persuasiveness of the evidence. Special masters may "inquir[e] into the reliability of testimony from expert witnesses. 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." Id. at 1325. The finding that an expert's opinion passes a minimal standard of reliability does not require acceptance of that expert's theory because "disputes about the degree of relevance or accuracy (above this minimum threshold [of reliability]) may go to the testimony's weight." i4i Ltd. Partnership v. Microsoft Corp., 598 F.3d 831, 852 (Fed. Cir. 2010)), cert. granted, 131 S. Ct. 647 (U.S. Nov. 29, 2010)(No. 10-290).

In evaluating expert testimony and scientific literature, special masters should analyze scientific literature "not through the lens of the laboratorian, but

instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu, 569 F.3d at 1379. "In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence." Broekelschen v. Sec'y of Health & Human Servs., 89 Fed. Cl. 336, 343 (2009), aff'd, 618 F.3d 1339 (Fed. Cir. 2010).

Generally, the Federal Circuit expects that a special master will present a reasonable basis for rejecting the opinion of one expert. Lampe, 219 F.3d 1361; Burns v. Sec'y of Health & Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993).

These standards will be used to determine whether Mr. Harris has established that he is entitled to compensation. For reasons explained in the following sections, the evidence does not support an award of compensation to Mr. Harris.

IV. Analysis – Causation / Significant Aggravation

For cases in which an injury is not listed on the Vaccine Injury Table, the statute permits petitioners to pursue two different causes of action. 42 U.S.C. §300aa-11(c)(1)(C)(ii)(I). The first, which is far more common, is based on a theory that the vaccinee "sustained . . . [an] injury or condition . . . which was caused by a vaccine." These cases are typically referred to as "causation in fact" cases.[4] The second theory is that the vaccine "had significantly aggravated . . . an injury or condition."

It appears that Jordan's case better fits the significant aggravation category. Mr. Harris recognizes that "Jordan had a pre-existing genetic defect." Pet'r Br. at 26. Mr. Harris argues that "the DTaP was a substantial contributing factor in significantly aggravating an underlying condition, a genetic defect." Id. at 25-26. Mr. Harris also argues that "Jordan's SCN1A mutation predisposed him to

[4] "Causation in fact" refers to petitioners' burden to establish the fact of causation. These cases can be contrasted with cases in which the Vaccine Act and the associated Vaccine Injury Table establish a presumption of causation. Mr. Harris does not maintain that Jordan suffered a Table injury.

suffering GEFS+ and that this genetic defect, and his DTaP vaccine, were substantial contributing factors to his suffering this seizure disorder." Id. at 14.

The elements of an off-Table significant aggravation case overlap with the elements of a causation-in-fact case. The comprehensive list of elements to show significant aggravation is:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a 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.

Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). The last three elements are derived from Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005). One special master has recommended evaluating "the last three Loving factors first." Hennessey v. Sec'y of Health & Human Servs., No. 01-190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009), motion for review denied, 41 Fed. Cl. 126 (2010). In evaluating a significant aggravation case, special masters should consider how the underlying pre-existing disease affected the person's health. Loving, 86 Fed. Cl. at 144 (placing burden on respondent after petitioners "successfully put forward such a prima facie case"); Gruber v. Sec'y of Health & Human Servs., 61 Fed. Cl. 674, 684 (2004) (discussing significant aggravation in the context of an on-Table claim).

Mr. Harris's case contains two separate, but related, ideas. First, Mr. Harris maintains that the DTaP vaccine affected Jordan's development. This argument is based upon a theory that "but for" the DTaP vaccine Jordan would have been different from whom he would have been if he had not received the DTaP vaccine. Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999)

(describing "but for" causation). This argument necessarily assumes that the SCN1A mutation by itself would not have caused Jordan to be as he is now. Whether the SCN1A gene played any role in Jordan's epilepsy is the second idea running through this case. Respondent maintains that "the SCN1A genetic mutation was the sole cause of Jordan's epileptic syndrome." Resp't Br. at 12.

The analysis begins with an evaluation of the role of the SCN1A gene. As set forth in section A, the evidence supports a finding that the sole cause of Jordan's epilepsy was the SCN1A mutation. This beginning assumes that Mr. Harris has met his burden of establishing that the acellular pertussis vaccination can affect seizure disorders. This assumption is generous because, as reviewed in section B, neither party's evidentiary presentation was particularly strong.

A. SCN1A Mutations and Seizure Disorders

The key dispute in this case is whether Jordan's SCN1A mutation was sufficient by itself to affect his development. The parties present opposite positions. Mr. Harris relies upon the testimony of Dr. Kinsbourne, who currently teaches psychology. Respondent relies upon the testimony of Dr. Wiznitzer, who currently practices pediatric neurology with an informal interest in Dravet's syndrome, and the testimony of Dr. Raymond, who researches genetically based neurological illnesses. The relative difference in experience among Dr. Kinsbourne, Dr. Wiznitzer, and Dr. Raymond is one reason for finding that the evidence establishes that the genetic mutation was the sole cause of Jordan's developmental change. The evidence about the causal role of the mutation is clear and convincing.[5] Before the different opinions are evaluated, a basic primer on genetics is set forth.

[5] Because the evidence weighs so heavily in favor of the position that respondent advocates, certain potentially unsettled legal issues are mooted. One issue concerns the burden of proof. Mr. Harris argues that respondent bears the burden of establishing the genetic mutation as the cause of Jordan's seizure disorder. Pet'r Br. at 13, 24-25, 47. Respondent argues that because Mr. Harris has not established a "prima facie" case, the burden to rebut the showing of causation never shifted to the government. Resp't Br. at 9-10, 18. The law on this point is unclear. Compare Althen, 418 F.3d at 1278 (listing three elements for petitioners' proof) with id. at 1281 (stating that "The remainder of the Stevens test – requiring…the elimination of other causes – is merely a recitation of this court's

1. Genetics[6]

Genes are found on chromosomes, which are part of a cell's nucleus. Genes are made of deoxyribonucleic acid ("DNA"). DNA contains two strands of nucleotides, which are joined to form the shape of a double helix. The four types of nucleotides are adenine, guanine, cytosine, and thymine, which are respectively abbreviated A, G, C, and T. Adenine always binds to thymine and guanine always binds to cytosine. Tr. 400-04; see also In re Fisher, 421 F.3d 1365, 1367 (Fed. Cir. 2005) (describing molecular genetics).

Genes instruct the body to build amino acids. A series of three bases (A, T, G, or C) encodes a specific type of amino acid. For example, the sequence C-A-A leads to the production of the amino acid known as glutamine. The sequence of

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well-established precedent"). Addressing whether Mr. Harris has succeeded in presenting evidence of such probative value such that the burden shifted to respondent is not necessary because even assuming that respondent bore the burden, respondent met the burden.

Further, there appears to be some dispute about whether the genetic mutation supplants the vaccine as a "cause" only when the genetic mutation is found to be the "sole cause." This dispute, too, is an academic point in this case. The evidence shows that the mutation was the sole cause.

In this case, the evidence about the causal role of the mutation is so powerful that the evidence sweeps away the legal disputes that could be important in other cases. The strength of the evidence is so great that this decision sometimes refers to the evidence as "clear" or "convincing." Labeling the evidence "convincing" is intended to refer to the value of the evidence and should not be confused with the burden of proof.

[6] Respondent's expert, Dr. Raymond, provided background information about genetics. In the absence of any serious dispute presented by Mr. Harris, Dr. Raymond's testimony is often the source for the following information about genetics. Dr. Raymond used a series of slides to assist the understanding of his testimony. Resp't Trial Exhibit 1.

For additional details about genetics in this context, see Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at *13-16 (Fed. Cl. Spec. Mstr. April 15, 2010), decision vacated and remanded, 95 Fed. Cl. 233 (2010).

three bases is known as a codon. More than one codon may code for the same amino acid. Tr. 416; Resp't Trial Exhibit 1 at 11-12.

The process leading to the creation of an amino acid includes several discrete steps, including transcription, splicing, transport, translation, and assembly. Resp't Trial Exhibit at 5. Dr. Raymond detailed these steps in his testimony, tr. 407-17, but a detailed recitation of them is not particularly necessary. It is sufficient to understand that the process is very complex and there is a chance for a problem or an error throughout the process. Tr. 417.

Changes in DNA are known as mutations. Mutations can be grouped into different categories. For example, mutations can occur in the portion of DNA known as an "intron," which is sometimes referred to as "junk DNA," or the portion of DNA known as an "exon," which contains the DNA used in protein synthesis.

Another way to classify DNA mutations is the type of mutation. In a point mutation, one base pair is replaced by a different base pair. These point mutations can be sub-classified into a nonsense mutation, meaning that the sequence of three base pairs does not code for any amino acid, or a missense mutation, meaning that the sequence of three base pairs codes a different amino acid, or silent mutation, meaning that the sequence of three base pairs still codes the same amino acid. Other types of mutations include insertion, which is the addition of one or more base pairs, and deletion, which is the removal of one or more base pairs. Resp't Trial Exhibit at 16-17.

Some changes in DNA do not alter the amino acid that is produced. For example, C-A-A leads to glutamine and C-A-G also leads to glutamine. Thus, a change from "A" to "G" in the third position of this codon is a silent mutation because the change does not affect the creation of the intended amino acid, which is glutamine. Tr. 421-22.

When the change in DNA produces an amino acid that resembles the intended amino acid, the change is called a conservative mutation. An example of a conservative mutation is a change from G-T-C, which codes for valine, to C-T-C, which codes for leucine. Valine and luecine have similar physical properties, so a change from valine to luecine may not affect the structure's function greatly. Tr. 422-23.

A more dramatic change in function follows other changes in DNA. For example, the early introduction of a stop codon prevents the complete construction of the intended amino acid. A frameshift mutation, which is what happens when one base pair is either added or deleted from the expected sequence, affects the remainder of the coding. When the sequence of genes is altered, the intended structure is not created as expected. Tr. 424-25.

2. How the Genetic Mutation Affected Jordan

Here, there is no dispute that Jordan suffers from a mutation in his SCN1A gene. Athena Diagnostic laboratories conducted genetic testing on Jordan and identified a mutation. Exhibit 6 at 51. Dr. Kinsbourne acknowledges that Jordan has a mutation. Tr. 59-60. Thus, the ensuing question is how this mutation affected Jordan.[7]

The evidence on this issue is divided into five categories. Paragraph a) discusses the opinion of Dr. Raymond. He is the most qualified expert to express an opinion. Dr. Raymond treats patients with genetic-based neurological disorders as part of his professional practice of medicine. He is, thus, far more qualified to offer opinions than Dr. Kinsbourne. Dr. Raymond's opinion is that Jordan's genetic mutation caused his developmental problems. Due to the persuasive value of Dr. Raymond's opinion, it is discussed first.

The second and third paragraphs ((paragraph b) and (paragraph c)) discuss Mr. Harris's attempt to counter Dr. Raymond's opinion. Paragraph b discusses at length the articles cited by Mr. Harris. Paragraph c evaluates the opinion presented by Dr. Kinsbourne. Neither the medical articles nor Dr. Kinsbourne's testimony has much probative force.

The fourth category is an analysis of an article published in 2010, the McIntosh article, that reported the results of a study involving children who had seizures after receiving a pertussis vaccination. This study corroborates the opinion expressed by Dr. Raymond that the SCN1A mutation is the sole cause of Jordan's epilepsy. The final paragraph (paragraph e) discusses statements made by

[7] A related, but slightly different, question of whether Jordan's initial fever affected his development is reserved until section IV.B.2.

doctors who treated Jordan. Their statements further reinforces Dr. Raymond's opinion.

a) Opinion of Dr. Raymond

Dr. Raymond opined that Jordan's SCN1A mutation caused his seizure disorder. Tr. 455; tr. 474-75. In reaching this conclusion, Dr. Raymond relied upon a methodology that appears consistent with the approach taken by authors in different articles. See Depienne and Berkovic; see also tr. 471-73. The methodology that Dr. Raymond used in reaching his opinion is also the same methodology that he uses when he counsels his patients. See tr. 487-89.[8] The similarity (or lack thereof) between the way an expert practices his profession and the opinions expressed in litigation may be considered when evaluating the expert's opinion. See Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 152 (1999).

The specific factors examined by Dr. Raymond were: (a) the type of mutation, (b) the location of the mutation, (c) what the mutation did, that is, what amino acids were substituted, and (d) the existence of precedent cases reported in the literature. See tr. 439-41; tr. 471-72; see also tr. 513 (stating "you have to use all the factors at your disposal"). These are discussed below.

- Type of mutation

Jordan's parents were tested to see whether either Jordan's mother or father had the same type of mutation that Jordan did. They did not. This means that Jordan did not inherit the mutation from either his mother or his father. Instead, the mutation arose "de novo." Tr. 59; tr. 152-53.

A de novo mutation is much more likely to present a severe disease for reasons that relate to whether the mutation occurs in a conserved region of the gene. Mulley at 538 (stating "De novo mutation associated with sporadic occurrence of disease is even stronger proof [of a causal relationship]. . . . De novo mutation is frequently observed in SMEI but as yet has not been observed in

[8] The same cannot be said for Dr. Kinsbourne because Dr. Kinsbourne has not treated a patient with an identified SCN1A mutation.

GEFS+."). In Dravet's syndrome, only a small number of cases are associated with inherited (or familial) mutations. Tr. 438.[9]

- Location of the mutation

Some portions of the human genome are relatively more important than other portions for proper functioning. Genetic sequences that appear in other species are considered to be very important because their continued presence suggests that a species could not function without the particular genetic sequence. Tr. 430; tr. 444-45; tr. 507, citing Depienne; tr. 556-58; see also Mulley at 539 (stating "If the variant postulated to have a pathogenic effect changes an amino acid at a position in the protein conserved through evolution (in the same sodium channel across species), . . . this is strong circumstantial evidence that the variant is pathogenic"); Turnbull at 2493. Clinical geneticists think that a mutation in a gene for a conserved region is more likely to cause a disease. Tr. 429.

- Details of genetic mutation

Jordan's genetic mutation is a change in the sequence of amino acids that control how DNA is transcribed into messenger RNA ("mRNA").[10] Because part of this process involves cutting (or splicing) long strands of DNA into smaller portions, this type of change is known as a "splice site" mutation. See tr. 407; tr. 410-12; Resp't Trial Exhibit A, slides 8-9.

A mutation at a splice-site tends to indicate a disease. Dr. Raymond's testimony on this point was consistent and forceful. Tr. 451-53 (stating, at page 453, for a splice-site mutation "you're going to have a disease"); tr. 530 (stating

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[9] When a parent passes a defective gene to a child, the child may display problems different from his or her parent due to a concept known as "mosaicism." Tr. 468; tr. 487. With SCN1A mutations, only about one percent of the identified mutations are mosaic mutations. Tr. 486; cf. tr. 368 (Dr. Kinsbourne's estimate that 90 percent of SCN1A mutations are de novo).

[10] Specifically, within intervening sequence 16 in Jordan's SCN1A gene, what should have been a "T" is actually a "C." Exhibit 6 at 51 (report from Athena Diagnostics); tr. 449; cf. tr. 59-60 (Dr. Kinsbourne's testimony that Jordan's mutation is at a splice site).

"you're going to see a disease with splice-site mutations"); tr. 531 (stating "if you see a splice-site mutation, you're going to have some alteration in the protein"); tr. 557. Dr. Kinsbourne did not really disagree with this assessment. Dr. Kinsbourne described Jordan's splice site mutation as a "legitimate SCN1A abnormality." Tr. 59.

- Precedent Cases

The factors discussed so far are points that can be considered in predicting how a mutation will affect a person based upon qualities of the genetic mutation itself. The next factor is based upon experience with living human beings. Information about how humans have been affected by a particular mutation has become available to clinical geneticists such as Dr. Raymond with the advent of more genetic testing and more reporting of results in databases.

Jordan's clinical mutation was reported in a 2009 article by Kumakura. Dr. Wiznitzer and Dr. Raymond opined that the subject of the Kumakura article has the exact mutation that Jordan has. The person in the Kumakura article has a clinical presentation that is similar to Jordan's clinical presentation. According to Dr. Wiznitzer and Dr. Raymond, this example shows that this particular mutation tends to control the person's development. Tr. 213-15 (Dr. Wiznitzer); tr. 450 (Dr. Raymond); tr. 560-61 (same).

Dr. Kinsbourne did relatively little to rebut the argument based upon the Kumakura case. When the undersigned solicited Dr. Kinsbourne's testimony about Kumakura in the rebuttal phase of the case, Dr. Kinsbourne suggested that the sample is "enormously biased." Tr. 366. Dr. Kinsbourne indicated that the sample is biased to include only children with severe diseases because other children may have the same mutation but have not been reported to a researcher assembling a database because these other children do not have a severe disease. Tr. 366; see also tr. 118-20 (Dr. Kinsbourne's testimony that a statistically significant study would involve "at least hundreds of thousands of subjects" to determine if the genetic mutations found in people with SMEI also are present in people who do not suffer from SMEI); tr. 568-70.

Dr. Kinsbourne's argument that the databases are biased to overreporting cases with severe disease is not persuasive for several reasons. First, Dr. Kinsbourne seems to assume that some people with the same mutation as Jordan

are normal. This assumption seems to be merely a theoretical construct and unlikely to be accurate because a de novo mutation at a splice site is likely to affect the person deleteriously. Second, Dr. Kinsbourne's criticisms about the bias in the databases are not shared by either Dr. Wiznitzer or Dr. Raymond, two doctors who routinely see patients with neurological problems based upon genetic mutations. Dr. Wiznitzer and Dr. Raymond explained that the genetic researchers consider and test for the possibility that a particular genetic change is actually a benign polymorphism.[11] Tr. 250-53 (Dr. Wiznitzer); tr. 462-64 (Dr. Raymond) tr. 501-03 (same); cf. tr. 426-28 (Dr. Wiznitzer's testimony about polymorphism). As such Dr. Kinsbourne's opinion seems not to be informed by how neurologists and clinical geneticists actually practice medicine and may be discounted.

Except for this argument that routinely used databases are actually biased, Dr. Kinsbourne did not address Dr. Raymond's specific points. Dr. Kinsbourne did not contest the following: (1) de novo mutations tend to be associated with disease more frequently than inherited mutations; (2) conserved regions of a gene are needed for functioning; and (3) a splice site mutation tends to be linked with a disease. Respondent's evidence on these points was quite convincing.

b) Articles Cited by Petitioner

Nevertheless, Mr. Harris maintains that a mutation in the SCN1A gene is not sufficient to cause a seizure disorder. Mr. Harris argues that "as Dr. Kinsbourne pointed out, the existing literature clearly suggests that an environmental trigger is also necessary to cause symptoms." Pet'r Br. at 24, citing Berkovic, Burgess, Kimura, Nieto-Barrera, Rhodes, Sell, Wallace, Yakoub, Gambardella, Depienne, and Claes (B); accord Pet'r Reply at 6-7 and at 17, citing many of the same exhibits.[12]

[11] A polymorphism is a harmless change in a gene. Tr. 35-36 (Dr. Kinsbourne); tr. 252 (Dr. Wiznitzer stating that benign polymorphism is a change in a gene that has no clinical relevance).

[12] This argument overlooks Dr. Kinsbourne's own testimony that he did not know whether every case of SMEI required an environmental trigger. Dr. Kinsbourne stated that some articles indicate that it is "possible" that an environmental factor triggers seizures. In this context, "possible" does not mean more likely than not. Tr. 120-22.

This argument overstates what the articles say. A more accurate generalization is that some authors have suggested that environmental factors may influence how a genetic mutation manifests clinically. Among these 11 articles, only two (Berkovic and Sell) discuss whether vaccines may be one environmental factor that affects a seizure disorder and Berkovic exonerates the vaccine. Further, none of the articles "clearly suggests" that an environmental factor is "necessary to cause symptoms." Mr. Harris's argument on this critical point is not persuasive.

A review of each article shows why Mr. Harris's reliance on that article is misplaced.

- Berkovic, Sell and Nieto-Barrera

The Berkovic article reports a retrospective examination of 14 patients who developed an encephalopathy within 72 hours of receiving a pertussis vaccine. (The article does not specify whether the patients received the whole-cell version or the acellular version.) DNA testing on the 14 patients revealed that 11 had a mutation in a SCN1A gene. According to the summary, "[c]ases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. These findings have important clinical implications for diagnosis and management of encephalopathy and, if confirmed in other cohorts, major societal implications for the general acceptance of vaccination." Berkovic at 488.

Berkovic and his co-authors reject the argument offered by Mr. Harris in this case, that the pertussis vaccine contributes to any seizure disorder, by stating:

> In the presence of SCN1A mutations, vaccination can still be argued to be a trigger for the encephalopathy, perhaps via fever or an immune mechanism. Our experimental design does not address this issue, but the role of vaccination as a significant trigger for the encephalopathy is unlikely for several reasons. First, although vaccination might trigger seizures as shown by the increased risk of febrile seizures on the day of triple antigen or MMR vaccination, there is no evidence of long-term adverse outcomes. Second, less than half our patients had documented fever with their first seizure,

> which indicates that fever is not essential. Third, our neuroimaging data showed no evidence of an inflammatory or destructive process. Finally, truncation and missense mutations reported in conserved parts of SCN1A have not been found in many hundreds of healthy patients. Thus, individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunised in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the SCN1A mutation.

Id. at 491 (footnotes deleted without notation).[13] Other than recognizing a theoretical possibility that vaccines could affect a seizure disorder, Berkovic does not advance the petitioner's claim. Actually, in stating that individuals with particular types of SCN1A mutations "seem to develop SMEI or SMEB whether or not they are immunised in the first year of life," Berkovic supports the respondent's argument.[14]

Berkovic is the foundation for another publication cited by Mr. Harris, the article by Erick Sell and Berge Minassian, which was published concurrently with the Berkovic article. The Sell and Minassian article is an editorial on Berkovic's findings and does not contain any original research. Tr. 80; tr. 127. Sell and Minassian stated that "Berkovic and colleagues ask a brilliant question: could some cases of encephalopathy attributed to vaccination have an alternative cause?" Sell and Minassian further stated that "The question was answered in the positive with the identification of mutations in SCN1A in 11 of 14 patients with purported vaccine encephalopathy." Sell at 465-66. This portion of the Sell and Minassian

[13] In a later paper, these authors stated that their experiment showed "that vaccination was wrongly blamed as an acquired cause of a genetic disorder, and the hypothesis that vaccination was the causal factor in our cohort could be rejected." McIntosh at 5. This article is discussed in paragraph (d) below.

[14] Dr. Kinsbourne dismissed Berkovic's conclusion as being "a subjective belief" because, according to Dr. Kinsbourne, Berkovic provided the belief "without giving us the reasons for the belief." Tr. 138-39. Respondent, in turn, accuses Dr. Kinsbourne of presenting "beliefs that you [Dr. Kinsbourne] have that are not supported by the literature." Tr. 138.

commentary indicates that the cause of the encephalopathy was actually the mutation, not the vaccine.

Mr. Harris relies upon a different passage from the Sell and Minassian commentary. Sell and Minassian employed another question-and-answer style, writing "Is the SCN1A mutation a predisposing factor waiting to be triggered by fever or other stress? Probably so." Sell at 466. Dr. Kinsbourne emphasizes this portion from the Sell and Minassian article. Exhibit 21 at 7. Sell and Minassian provided only one basis for their conclusion that fever or other stress triggers the SCN1A mutation and that source is the Nieto-Barrera article.

Reliance on the Nieto-Barrera article is not logical. The brilliance – to borrow a word from Sell and Minassian – of the Berkovic study was to reexamine cases in which the cause of an encephalopathy was attributed to a vaccine. Berkovic discovered that in 11 of 14 cases the person suffered from an SCN1A mutation, opening the possibility of a different cause. This change in thinking started by Berkovic raises questions about the usefulness of studies that did not account for the presence or absence of a genetic mutation. The Nieto-Barrera article is one such report because it was done before the SCN1A gene was discovered. Tr. 126; tr. 465. Without knowing whether the subjects of the Nieto-Barrera article also had a mutation in the SCN1A gene, it is difficult to conclude that the gene did not cause the seizure disorder for those children. See exhibit E (Dr. Raymond's report) at 6.[15]

[15] A separate reason for not relying upon the Nieto-Barrera study comes from Dr. Wiznitzer. He pointed out that Nieto-Barrera provides one reference for stating that the whole cell pertussis vaccine affected the children's brain. Tr. 290. That reference is a 1990 paper authored by Dr. Menkes and Dr. Kinsbourne. Nieto-Barrera at 6 & reference 20. According to Dr. Wiznitzer, the underlying Menkes and Kinsbourne paper, itself, is predominantly speculative. Tr. 290-91. Dr. Kinsbourne defended his article. Tr. 360-63. Because neither the 1990 Menkes and Kinsbourne paper nor the articles cited in that paper were filed into the record, evaluating Dr. Wiznitzer's criticism is not possible.

- Rhodes and Wallace

Mr. Harris cites to the article by Rhodes as "clearly suggest[ing] that an environmental trigger is also necessary to cause symptoms." Pet'r Br. at 24. In his report, Dr. Kinsbourne quoted this article as suggesting the defect in a sodium channel combines with something else to produce the severe neurological problems:

> The disparity in clinical severity between GEFS+ and SMEI probably requires explanations other than just differences in channel behavior. We would like to speculate that the severe neurological consequences of SMEI are caused by a combination of sodium channel dysfunction (either gain or loss of function) with predisposing genetic or developmental factors that lead to a great chance of neuronal injury. In this model, the sodium channel defect creates the initial seizure predisposition, but concomitant excitotoxicity is the direct cause for other neurological features of the disorder.

Exhibit 21 (Dr. Kinsbourne's report) at 5 (quoting Rhodes at 11151).

Dr. Kinsbourne's citation to Rhodes for the idea that the genetic defect in the sodium channel is not sufficient to cause neurological damage is odd for two reasons. First, the "extra" factors that Rhodes lists are "predisposing genetic or developmental factors." Rhodes at 11151. Rhodes does not elaborate upon what "developmental factors" could affect the clinical presentation. See id. tr. 72 (Dr. Kinsbourne stating that Rhodes does not say what causes the encephalopathy). Rhodes does not mention vaccines. Tr. 136. Second, when Dr. Kinsbourne was asked whether he was advancing Rhodes's theory, Dr. Kinsbourne stated that "I am not basing myself on Rhodes in my opinion." Tr. 73. Consequently, Dr. Kinsbourne's statements seem to undercut Mr. Harris's citation to Rhodes.[16]

[16] Apart from the limited use of Rhodes by Dr. Kinsbourne, Dr. Raymond provided additional reasons that Rhodes does not support the assertion that an environmental trigger is needed. See tr. 520-23; tr. 554-55.

Rhodes is the basis of a commentary by Wallace, which Mr. Harris also cites in his brief. In Dr. Kinsbourne's report, he quoted Wallace as stating "The fact that similar mutations cause two different phenotypes implies that other environmental or genetic factors are associated with SMEI." Exhibit 21 at 5 (quoting Wallace at 18). Dr. Kinsbourne was not asked to develop this point in his testimony.

The statement in Dr. Kinsbourne's report is more limited than the assertion in Mr. Harris's brief, which is that Wallace "clearly suggests that an environmental trigger is also necessary to cause symptoms." Pet'r Br. at 24. Wallace does not use the term "trigger" and Wallace says that "environmental or genetic factors" could influence whether the genetic mutation in the SCN1A gene develops into either SMEI or GEFS+.

Additionally, the usefulness of Wallace's commentary is limited by its publication in 2005 before the latest discoveries about sodium channel mutations were made. She recommended "[t]horough investigation of genetic and environmental modifying factors . . . to determine their influence on disease manifestation and progression." Wallace at 19. Since the writing of that commentary, more research has been done.

- Burgess, Kimura, Gambardella

Other articles cited in Mr. Harris's brief also have limited application because of when the articles were written. For example, in 2005, Burgess wrote "[t]he degree to which these genetically initiated phenotypes are shaped by environmental influences is unclear." Burgess at 53. This statement is quoted by Dr. Kinsbourne. Exhibit 21 at 5. In his testimony, Dr. Kinsbourne cited Burgess only for the proposition that some articles "describe the potential environmental effect." Tr. 70.

Kimura is another article from 2005. Kimura reported a family in which a parent has a genetic abnormality without significant problem but his or her children, who also have the genetic abnormality, have more severe problems. Kimura suggested that a reason for the difference in clinical presentation was "the existence of genetic or environmental factors other than SCN1A mutations [that] may modify SMEI phenotypes." Kimura at 425. In his testimony, Dr.

Kinsbourne's only discussion about the Kimura article was that "genetic or environmental factors" may affect the degree of seizure activity. Tr. 69.

The reports from Dr. Wiznitzer and Dr. Raymond explained that Kimura's case report is probably an example of what is now termed "mosaicism." Exhibit C (Dr. Wiznitzer's report) at 4, citing Morimoto at 1735 (stating "We here propose that the yet-undetected mosaicisms of the corresponding SCN1A mutation in parents may also play critical roles in some of these cases"); exhibit E (Dr. Raymond's report) at 5, citing, among other articles, Morimoto. Dr. Raymond also discussed mosaicism in his testimony, explaining that mosaicism occurs when a child has more copies of a defective gene than his or her parent. Tr. 468-70.

Inherited genes also limit a statement from another article that Mr. Harris cites in his brief, the article by Antonio Gambardella and Carla Marini. Gambardella and Marini indicate that a "complex interaction between genetic and acquired factors modulate disease severity of produced phenotypes." Gambardella at 22. Dr. Raymond explained that this statement makes sense in the context of inherited disorders and does not explain what happens with a de novo mutation, such as the one Jordan has. Tr. 490-94.

- Depienne

Depienne and colleagues reported a case that suggested "that the variation in clinical presentation is not intrinsic to the mutations themselves but rather to the interaction with other yet unidentified genetic or environmental factors." Depienne at 10. Dr. Kinsbourne quoted this aspect of this article in his testimony. Tr. 91. However, Dr. Raymond stated that Depienne's statement needs to be placed in the context of the specific type of mutation reported by Depienne. Tr. 506-10.

- Lossin and Claes

Mr. Harris also cites an article by Claes. Pet'r Br. at 24. The foundation for the Claes article is the article by Lossin. Tr. 82-83. In 2008, Dr. Lossin cataloged more than 300 mutations in the SCN1A gene. According to Dr. Kinsbourne, Lossin tried to determine whether the type of genetic abnormality causes SMEI (versus a genetic abnormality that causes GEFS+) and found that he could not. Tr. 82-83 (Dr. Kinsbourne). The implication of this testimony was that a mutation in

the gene does not determine the outcome, further implying that something other than the genetic mutation is needed to explain the clinical presentation.

Dr. Kinsbourne is correct that Dr. Lossin struggled to organize reports of genetic mutations into a coherent pattern. One reason for this struggle is important and appears to have been overlooked by Dr. Kinsbourne. Dr. Lossin states that a "complication is the lack of uniform mutation nomenclature, with different groups reporting their findings in reference to different $Na_v1.1$ splice variants." Dr. Lossin's article and its associated online database attempts to solve this problem by "compil[ing] an up-to-date, standardized mutation database that will facilitate future work with $Na_v1.1$ mutations." Lossin at 2. Dr. Lossin's article does not suggest, even remotely, that the problem with trying to correlate genetic mutations with clinical expressions is due to environmental influences.

Lossin's online database, in turn, was used by Claes in the article cited by Mr. Harris in further support of the proposition that "the existing literature clearly suggests that an environmental trigger is also necessary to cause symptoms." Pet'r Br. at 24. Claes analyzed a database containing more than 600 variants. In this analysis, Claes reported that some genes had different outcomes. Claes offered the following explanation: "The underlying factors that might explain all these phenotypic differences are environmental factors, e.g. viral infections . . . differences in genetic background, mutations in modifier genes either ameliorating or aggravating the phenotype . . . or mosaicism." Claes (B) at E911 (citations omitted).[17] This is the portion emphasized by Dr. Kinsbourne. Tr. 85. Of the four possible influencing factors, one is environmental and the other three relate to genes. Tr. 130-32.

Claes, however, does not emphasize the role of the environment. Claes states that "genotype-phenotype correlations seem to be fairly strict." Claes (B) at E910. This statement is relied upon by Dr. Wiznitzer for his opinion that he can use past experience with genetic mutations to predict how another child with the same mutation will develop. Tr. 250-51.

[17] Dr. Raymond stated that Claes's statement explains why cases of GEFS+ vary. Tr. 483-86; tr. 547-48 ("I would emphasize again that this is a situation with a GEFS mutation and a slightly severe phenotype in a different patient, and they're trying to reconcile the rare patient.").

- Yakoub

Mr. Harris also cites an article by Yakoub. Yakoub. Dr. Kinsbourne mentioned that this article looked at vaccinations and SMEI in an "incidental way." Tr. 80; accord tr. 126-27. Given that Dr. Kinsbourne does not emphasize this report and given that the article was published before the SCN1A gene was discovered, Yakoub has negligible weight. See tr. 230 (Dr. Wiznitzer stating that older articles may not be worth much weight).

- Summary of Analysis of Articles Cited by Mr. Harris

In his brief, Mr. Harris makes the rather broad statement that "as Dr. Kinsbourne pointed out, the existing literature clearly suggests that an environmental trigger is also necessary to cause symptoms." Pet'r Br. at 24. The literature cited by Mr. Harris does not support this proposition. The articles do not talk about environmental triggers as necessary to cause symptoms.

Given that Mr. Harris's theory is that a specific factor from the environment, the administration of the DTaP vaccine, affected Jordan's development, Mr. Harris should have presented persuasive evidence that environmental factors influence the expression of the SCN1A gene. Mr. Harris did not. He actually elicited relatively little testimony from Dr. Kinsbourne about these articles. The short testimony from Dr. Kinsbourne skipped over important details and qualifications within the articles that respondent's experts addressed. The evidence does not support the argument made in Mr. Harris's brief.

c) Testimony of Dr. Kinsbourne

Even without support from any published literature, Mr. Harris may prevail by relying upon other evidence. See Althen, 418 F.3d at 1280. In this case, the other evidence submitted by Mr. Harris is the testimony of Dr. Kinsbourne.

Dr. Kinsbourne's testimony is not persuasive. Dr. Kinsbourne does not have any practical experience in treating people with SCN1A mutations. Dr. Kinsbourne essentially stopped practicing pediatric neurology in 1981. Dr. Kinsbourne's lack of practical experience was one factor given by a special master in finding his testimony not persuasive in a decision denying compensation for a condition known as tuberous sclerosis (TS) that was issued in 2000. Flanagan v. Sec'y of Health & Human Servs., No. 90-1126V, 2000 WL 1207256, at *13 (Fed.

Cl. Spec. Mstr. Aug. 4, 2000). The special master described the difference in experience levels between the respondent's expert (Dr. Holmes) and Dr. Kinsbourne:

> When choosing between Drs. Holmes and Kinsbourne in holding what Ashley's TS sequelae would be, the court really cannot rely on Dr. Kinsbourne who has had no clinical experience in ten years and does not treat TS or any patients. Dr. Holmes both teaches at a well-established medical school and has a subspecialty in epilepsy. He cares for patients, including TS patients. It would be unreasonable, arbitrary, and capricious for the undersigned not to give greater weight to a man as accomplished as Dr. Holmes is in this field.

Id. at *16.

Both the Court of Federal Claims and the Federal Circuit affirmed this decision. In the context of finding that the special master's decision denying compensation was not arbitrary or capricious, the Court of Federal Claims quoted a portion of the special master's decision that stated Dr. Kinsbourne "has not been in practice for ten years." Flanagan v. Sec'y of Health & Human Servs., 48 Fed. Cl. 169, 173-74 (2000). Similarly, the Federal Circuit cited this portion of the Court of Federal Claims's decision and stated that the "special master properly considered the relevant evidence, drew plausible inferences, and stated a rational basis for the decision." Turner v. Sec'y of Health & Human Servs., 268 F.3d 1334, 1338-39 (Fed. Cir. 2001).[18]

The special master's reasoning regarding Dr. Kinsbourne's lack of practical experience remains valid. If anything, the passage of time has only heightened the concern about Dr. Kinsbourne's knowledge about current issues in pediatric

[18] At the Federal Circuit, Flanagan was consolidated with another case known as Turner and the published decision of the Federal Circuit in Flanagan is under the Turner caption.

neurology.[19] Dr. Kinsbourne was not a practicing pediatric neurologist in 2000, when the SCN1A mutation started being linked to GEFS+ and SMEI. See Mulley at 535. This means that approximately one decade has passed during which advancements about SCN1A were made when Dr. Kinsbourne was not practicing pediatric neurology. Instead, Dr. Kinsbourne has been working as a professor teaching psychology to non-medical students. Tr. 11-13; tr. 156. Although Dr. Kinsbourne represents that he read literature on SCN1A to support his work as an expert witness, tr. 104-05, it is difficult to see how Dr. Kinsbourne's efforts can equal the knowledge gained by Dr. Wiznitzer and Dr. Raymond.

For both Dr. Wiznitzer and Dr. Raymond, the study of neurologic problems associated with genetic abnormalities is a regular part of their full-time careers. Both Dr. Wiznitzer and Dr. Raymond counsel patients with genetic mutations that cause neurological problems. Tr. 185-86 (Dr. Wiznitzer); tr. 209-10 (same); tr. 395-96 (Dr. Raymond). Their professional duties give them a depth of knowledge that is not matched by Dr. Kinsbourne. For example, Dr. Wiznitzer attended an international conference about SCN1A just before the hearing in this case.

Given Dr. Raymond's and Dr. Wiznitzer's credentials, their insights merit consideration. Dr. Wiznitzer and Dr. Raymond expressed the opinion that the SCN1A gene was the cause of Jordan's epilepsy. Tr. 223 (Dr. Wiznitzer); tr. 227 (Dr. Wiznitzer stating "[i]n my opinion there is no evidence whatsoever that the DTAP vaccine plays any role in this clinical disorder."); tr. 455 (Dr. Raymond); tr. 474-75 (same). Mr. Harris presented no persuasive reason for disagreeing with these opinions. See Pet'r Br. at 23-24, 39-40; Pet'r Reply at 14-15, 19-20.

The opinion of Dr. Wiznitzer and Dr. Raymond that the SCN1A gene caused Jordan's seizure disorder is difficult to challenge because this opinion is consistent with several medical articles. For example, the Berkovic article, which was cited by Mr. Harris, concluded that the authors did not think that "avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbor the SCN1A mutation." Berkovic at 491. Claes, which was also cited by Mr. Harris, states that "genotype-phenotype correlations seem to be fairly strict." Claes (B) at E910. This is the same conclusion reached in another article: "detailed analyses of all published patients for whom sufficient clinical

[19] Earlier in his career, Dr. Kinsbourne made some remarkable contributions to the field of pediatric neurology, including the first report of opsoclonus-myoclonus syndrome (also known as Kinsbourne's syndrome).

and genetic information is available clearly demonstrates phenotype/genotype correlation." Ceulemans (2004a) at 241.

d) McIntosh Article

These articles are a sufficient basis for finding that the opinions of Dr. Raymond and Dr. Wiznitzer are reliable. The McIntosh article reinforces this finding.[20] Researchers including Ingrid Scheffer, who spoke at the conference on Dravet's syndrome attended by Dr. Wiznitzer, and Samuel Berkovic, who was the first-named author on another paper, "analyzed medical and vaccination records to investigate whether there was an association between vaccination and onset of seizures" in patients with Dravet's syndrome who had mutations in the SCN1A gene. McIntosh at 1. These researchers found that a number of children had seizures within two days of receiving a dose of the whole or acellular pertussis vaccine. Another group of children did not have seizures within two days of receiving a vaccination. The groups were respectively called the "vaccine-proximate group" and the "vaccine-distant group." The researchers assessed whether the clinical outcome differed between the two groups. In conducting this experiment, the McIntosh researchers tested a hypothesis that a pertussis vaccine affected the children's development; testing is a factor that a special master may consider in assessing the reliability of an expert's opinion. Terran, 195 F.3d at 1316 n.2 (citing Daubert).

When McIntosh tested to see whether a vaccine affected the outcome of children with SCN1A mutations, the experiment showed that there was no effect. The authors stated that:

> although vaccination might sometimes seem to trigger the onset of Dravet's syndrome, 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

[20] Respondent was permitted to file this article after the hearing because it was published in May 2010, which was after the hearing. Order, filed May 26, 2010.

> group is not consistent with vaccination itself affecting the severity of the disorder.

Id. at 5-6. Although Dr. Kinsbourne responded to the McIntosh article (exhibit VV; exhibit 74, tab A), his response did not explain why the conclusion of the researchers was wrong. Thus, McIntosh further confirms the reliability of the opinions offered by Dr. Wiznitzer and Dr. Raymond.

e) Jordan's Medical Records and Statements of Treating Doctors

The previous sections have discussed the opinions expressed by Dr. Kinsbourne, Dr. Wiznitzer, and Dr. Raymond as well as the articles on which they rely. An additional source of evidence in this case is the collection of medical records about Jordan. These records support the finding that Jordan's epilepsy was caused by the SCN1A mutation.

The most valuable information comes from evaluations by Dr. Wallerstein and Dr. Chung. Both Dr. Wallerstein and Dr. Chung treated Jordan after his genetic mutation was discovered. Additionally, both Dr. Wallerstein and Dr. Chung have expertise in genetics. Dr. Wallerstein is the chief of genetic services for Hackensack University Medical Center. Dr. Chung is the director of clinical genetics at Morgan Stanley Children's Hospital, which is affiliated with Columbia University Medical Center.

Dr. Wallerstein stated that Jordan has a "splice site mutation in this gene [the SCN1A gene] that is predicted to be associated with seizures." Dr. Wallerstein also stated that the "SCN1A gene is associated with severe myoclonic epilepsy and also with generalized febrile seizures." Exhibit 6 at 18.

Dr. Chung also reviewed Jordan's case. Dr. Chung "reviewed the molecular genetics of SCN1A" and the information about Jordan's mutation. She stated that "[a]lthough I do not have a specific precedent based on other individuals with his exact mutation, I believe that this is more likely to be associated with the GEFS+ end of the disease spectrum rather than SMEI or ICEGTC."[21] Dr. Chung

[21] Although Dr. Chung mentioned that she did not locate any precedent for Jordan's mutation, a case was included in a publication by Kamakura in 2009.

expressed hope that continued research on SCN1A mutations may offer additional therapies to Jordan in the future. Exhibit 6 at 44-45.

Thus, Dr. Wallerstein and Dr. Chung, both of whom are experts in the field of genetics, focused their attention on the SCN1A gene. Neither Dr. Wallerstein nor Dr. Chung suggested that DTaP vaccine affected Jordan's outcome. Whether Dr. Wallerstein was aware that the vaccination preceded Jordan's first seizure by a few hours is not readily apparent, but Dr. Chung mentioned the immunizations in her recitation of Jordan's history. Exhibit 6 at 43.

The reports of Dr. Wallerstein and Dr. Chung are consistent with the approach taken by Dr. Wiznitzer and Dr. Raymond. They testified that a clinical geneticist would consider, among other factors, whether the mutation was inherited or arose de novo and whether the mutation had been reported in any preceding cases. Tr. 267 (Dr. Wiznitzer stating that "I can predict [a child's outcome] if I have previous mutations that have been described"); tr. 448-54. Thus, the reports from Dr. Wallerstein and Dr. Chung, which mention these factors, tend to validate the methodology employed by Dr. Wiznitzer and Dr. Raymond.[22]

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[22] Mr. Harris argues that Jordan's "treating physicians linked the vaccine and the seizure." Pet'r Reply at 11. This argument is based upon some reports showing that the doctors were aware that Jordan received the vaccine hours before he had the first seizure. E.g. exhibit 4 at 2, exhibit 4 at 41 (discharge summary), exhibit 7 at 46-47 (admission summary for Jordan's second seizure).

These records do not establish that Jordan's treating doctors stated that the vaccine caused the seizure. These records actually show that the doctors recognized the temporal sequence in that the vaccine preceded the seizures. A temporal sequence differs from a causal relationship as discussed in one of the cases testing the theory that vaccines cause autism. In that case, the special master found that the treating doctor described a temporal relationship, not a causal relationship, between a vaccination and the determination of autism. Cedillo v. Sec'y of Health & Human Servs., No. 98-916V, 2009 WL 331968, at *128 (Fed. Cl. Spec. Mstr. Feb. 12, 2009). Upon a motion for review, the Court of Federal Claims found that "the Special Master properly evaluated these records." Cedillo, 89 Fed. Cl. at 176. The Federal Circuit affirmed this analysis. Cedillo, 617 F.3d at 1347.

3. Summary Regarding SCN1A Gene

The primary issue in this case is the extent to which the mutation in Jordan's SCN1A gene affected his epilepsy. The evidence convincingly shows that this mutation determined his epilepsy. Jordan's mutation arose de novo and occurred in a conserved region of the gene, specifically at a splice site. These undisputed characteristics about Jordan's gene meant, according to Dr. Raymond, that Jordan was "going to have a disease." Tr. 453.

Mr. Harris's attempts to controvert the opinions expressed by Dr. Raymond and Dr. Wiznitzer were not successful. Mr. Harris relied upon the testimony of Dr. Kinsbourne, who has not knowingly treated a child with an SCN1A mutation. To the extent that Dr. Kinsbourne's opinion has been informed by reading medical articles, the articles generally do not support the arguments advanced by Mr. Harris. The studies that investigated whether a pertussis vaccine affected the development of a person with an SCN1A mutation concluded that the vaccine did not cause the epilepsy. Berkovic, McIntosh. The finding in the present decision is in accord with those studies.

The finding that the SCN1A mutation was solely responsible for causing Jordan's epilepsy resolves this case. This finding necessarily implies that the DTaP vaccine did not affect Jordan's epilepsy. For the sake of completeness, this subsidiary issue is addressed below.

B. DTaP and Seizure Disorders

Even if the evidence showed that the SCN1A mutation was not the sole cause of Jordan's epilepsy, this finding would not entitle Mr. Harris to compensation automatically. Mr. Harris would still need to establish, by preponderant evidence, "a medical theory causally connecting such a significantly worsened condition to the vaccination." Loving, 86 Fed. Cl. at 144. This particular element is derived from the test announced in Althen, 418 F.3d at 1278. Mr. Harris maintains that he has met his burden of proof by presenting a plausible theory through Dr. Kinsbourne. Pet'r Br. at 14-20. The theories articulated by either Dr. Kinsbourne or by Mr. Harris, however, lacked clarity.

Dr. Kinsbourne asserts two ideas. Tr. 73 (Dr. Kinsbourne's testimony that "when I come to my opinions as to mechanism, I'm going to mention two factors."). One theory is that DTaP vaccine can cause a fever, a fever can cause an

initial seizure, and the onset of one seizure makes additional seizures more likely. Another theory is that the DTaP vaccine affects cells of the central nervous system to make seizures more likely. This theory seems not dependent upon the presence of a fever. Mr. Harris's brief asserts both ideas. Pet'r Br. at 15, citing exhibit 21 (Dr. Kinsbourne's report) and at 17, citing tr. 49-51 (Dr. Kinsbourne's testimony).

Each theory will be analyzed separately. As set forth below, the theory that the vaccine causes a fever received relatively little attention in the parties' briefs. The other theory – the theory that the DTaP vaccine damages parts of the nervous system – was the topic on which the experts and the attorneys focused. Because the parties emphasized this theory, this decision takes up that theory first.

1. Theory That Acellular Pertussis Vaccine Affects the Central Nervous System

Mr. Harris devotes much attention to attempting to establish that the acellular pertussis vaccine can damage the central nervous system. Mr. Harris relies upon Dr. Kinsbourne, who presented a theory that can be divided into three discrete propositions. The foundation for Dr. Kinsbourne's theory is that the acellular form of the pertussis vaccine still contains pertussis toxin. Assuming that this foundation is established, the next step is that some (toxic) portion reaches the brain. The third and final step is that the pertussis toxin damages the neurons, which are cells in the brain.

The evidence relevant to each of these three steps is briefly discussed below. This discussion may demonstrate that the decision in this case was made after consideration of the "record as a whole." 42 U.S.C. § 300aa—13(a). The discussion also may bring to counsel's attention some of the gaps in petitioner's and respondent's attempts to demonstrate that the acellular pertussis vaccine can cause or does not cause neurological injury. Whether the acellular pertussis vaccine causes neurological injuries is an issue that appears occasionally in Vaccine Program cases, e.g., Sucher v. Sec'y of Health & Human Servs., No. 07-58V, 2010 WL 1370627, at *38 (Fed. Cl. Spec. Mstr. March 15, 2010), and, therefore, warrants some analysis in this decision.

This decision, however, does not reach a conclusion regarding whether preponderant evidence in this case demonstrated that the acellular pertussis vaccine can cause neurological damage. The evidentiary presentations were lacking in various respects, such as the expression of opinions outside a person's areas of

expertise, a lack of disclosure of opinions before the hearing, and a lack of pre-trial disclosure of the basis for opinions. These flaws indicate that the record in this case was not as developed as it could have been and suggest that any conclusion would necessarily be tentative. Furthermore, in light of section A's finding that the SCN1A gene was the sole cause of Jordan's epilepsy, even a finding that the acellular pertussis vaccine can cause the harm ascribed to it by Mr. Harris would not affect the outcome of Mr. Harris's claim.

a) Step 1: Acellular Pertussis Vaccine Versus Whole-cell Pertussis Vaccine

An initial step in Dr. Kinsbourne's theory is that the acellular pertussis vaccine contains elements that are harmful to the nervous system. Pet'r Br. at 15. Dr. Kinsbourne stated that the process by which pertussis toxin is made safer, a process called toxoiding, is sometimes incomplete. The lack of complete toxoiding leaves some dangerous pertussis toxin in the acellular vaccine. Tr. 25-27; tr. 154-55.

Evaluating whether Dr. Kinsbourne's assertions are reliable is difficult. Any discussion about toxoiding would be more informed by someone with expertise in pharmacology and Dr. Kinsbourne recognized that he lacked that expertise. Tr. 353-54. Further, although Mr. Harris presented articles to support Dr. Kinsbourne's assertions regarding toxoiding (Corbel; Cyr; Gomez), there was no testimony about them. The significance of these articles was disputed by the parties. Compare Pet'r Resp., filed Nov. 5, 2009, with exhibit TT (supplemental report from Dr. Wiznitzer, stating that the articles were "not accurately cited.") at 1.

On this record, it makes little sense to address whether the toxoiding process completely inactivates all pertussis toxin. The issue was not presented well.

b) Step 2: The Blood-Brain Barrier

If it is assumed that a biologically meaningful amount of a toxic substance remains after toxoiding, the next question is how would this substance reach the brain? This question arises because the acellular pertussis vaccine is not injected into the brain. Instead, the acellular pertussis vaccine is given in an extremity. Although arms and legs are connected to the brain via the circulatory system, a barrier usually separates the brain from the blood.

Dr. Kinsbourne asserted that a fever can increase the permeability of the blood-brain barrier. Tr. 353; tr. 360. Dr. Kinsbourne did not cite any articles in support of his assertion during this testimony. When Mr. Harris asked Dr. Raymond during cross-examination whether he thinks that fever can increase the permeability of the blood-brain barrier, Dr. Raymond responded that he did not know because he was not aware of any studies on this question. Tr. 517.

The permeability of the blood-brain barrier is another topic on which Mr. Harris's evidence is questionable. If Mr. Harris did not present preponderant evidence that the pertussis vaccine crosses the blood-brain barrier, then the theory that he advances would not be persuasive. See Moberly v. Sec'y of Health & Human Servs., No. 98-910V, 2005 WL 1793416, at *28 (Fed. Cl. Spec. Mstr. June 30, 2005) (stating "the special master decides that the utility of Dr. Kinsbourne's blood brain barrier theory as an element of proof of causation-in-fact in this case is dubious"), motion for review denied, 85 Fed. Cl. 571, 605 (2009) (finding that special master did not act arbitrarily or capriciously in rejecting the untested theory about the blood brain barrier), aff'd, 592 F.3d at 1324 (rejecting petitioner's argument that Dr. Kinsbourne's theory involving the blood brain barrier should have been credited).

The evidence in Mr. Harris's case seems to be about the same as the evidence in Moberly. Mr. Harris did not present any evidence that would shore up Dr. Kinsbourne's assertion that a (toxic) portion of the acellular pertussis vaccine would cross into the brain. The present case contains just Dr. Kinsbourne's unsupported assertion, which a fact finder may reject as unpersuasive. Cedillo, 617 F.3d at 1339 (citing Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)). Thus, it appears that a decision rejecting Mr. Harris's claim on this basis would be in accord with the Moberly precedent.

c) Step 3: The Effects of Pertussis Toxin on Neurons

Even if it were assumed that the acellular pertussis vaccine contained a biologically meaningful amount of pertussis toxin after toxoiding and that some portion crossed the blood-brain barrier to reach the brain, Mr. Harris must take another step. He must link the pertussis toxin to damage in Jordan's nervous system. For this step, Dr. Kinsbourne's attempt to articulate even a minimally coherent theory was largely unsuccessful. Repeatedly, Dr. Kinsbourne asserted

one theory, was presented with information that made his asserted theory implausible, and then switched to another theory.

Initially, Dr. Kinsbourne linked the pertussis toxin to sodium channels through a substance known as a G protein.[23] His first report stated that pertussis toxin "uncouples the G protein receptors. . . [that] have inhibitory control over voltage gated sodium channels." Exhibit 21 (Dr. Kinsbourne's report) at 8.[24]

At the hearing, Dr. Kinsbourne did not offer this opinion. Instead, Dr. Kinsbourne maintained that the SCN1A gene affects neurons that inhibit seizures and that pertussis's effect on G proteins also affects inhibitory neurons. Tr. 33-34. Dr. Kinsbourne said "we have what we would call the converging influence of two different sources of abnormality." Tr. 34. By saying that "two different sources of abnormality" converge, Dr. Kinsbourne was presenting a theory different from the one he had presented in his expert report.

When asked to support his statement that "there [is] a converging influence of the G-protein in the sodium channel," Dr. Kinsbourne identified two articles neither of which had been filed into the record before the hearing. Tr. 37-41; see also tr. 113-14. After the hearing, Mr. Harris filed the two articles cited by Dr. Kinsbourne during his testimony,Catterall and Thalmann.

During a recess in the hearing, Dr. Wiznitzer reviewed the Thalmann article, which he happened to have available on a laptop computer. This review permitted Dr. Wiznitzer to testify that "the Thalmann article says nothing about sodium

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[23] G proteins are proteins that affect channel gating between the surface of cells and the interior of cells. See Dorland's Illustrated Medical Dictionary (31st ed. 2007) at 1556. There are different types of G proteins. Tr. 288 (Dr. Wiznitzer); tr. 312-13 (same); see also exhibit UU (supplemental report from Dr. Raymond) at 1 (stating "G proteins are an expansive and important group of regulatory proteins in cell biology. Different G-proteins may be used in the same cell to carry out a variety of specific cell functions as well as highly specialized functions only found in certain cell types.")

[24] Later, after the hearing, Dr. Kinsbourne stated that "I make no claim that pertussis toxin necessarily implicates those ion channels that are under SCN1A control." Exhibit 73 at 3.

channels." Tr. 242.[25] In rebuttal, Dr. Kinsbourne stated, erroneously, "I never said it [the Thalmann study] was a sodium channel." Tr. 375.

After Dr. Wiznitzer explained that the Thalmann article did not involve sodium channels, Dr. Kinsbourne switched approaches. In the rebuttal phase of his testimony, Dr. Kinsbourne presented a theory that the Thalmann article showed that G-proteins control inhibitory neurons with a potassium channel, not a sodium channel.[26] Tr. 375-76.

The theory that the pertussis toxin damages potassium channels is a theory that Dr. Kinsbourne did not offer before his rebuttal testimony. His original report did not use the term "potassium." See exhibit 21. Without any mention of potassium channels, Dr. Kinsbourne discussed sodium channels in his direct testimony. Tr. 37-41; tr. 113-14. Whenever his earlier testimony was about a "convergence" of forces, this testimony was in the context of sodium channels.

Again, evaluating Dr. Kinsbourne's opinion is difficult because Dr. Kinsbourne's opinion about how pertussis toxin affects neurons changed throughout the case. Mr. Harris has not demonstrated the reliability of Dr. Kinsbourne's first theory, which was that the pertussis toxin damages the G-proteins that control sodium channels. Mr. Harris also has not demonstrated the reliability of Dr. Kinsbourne's second theory based, which was based upon the Catterall and Thalmann articles. This leaves the theory based upon a potassium channel, which was raised only in rebuttal. An evaluation of this theory based upon this record would not be wise. Dr. Raymond stated that "My education, training, and experience indicates that these are very complicated systems, and to

[25] Because the Catterall article was not available to respondent's experts until after the hearing, they did not comment on the Catterall article until they filed supplemental reports after the hearing. Both Dr. Wiznitzer and Dr. Raymond commented that Catterall experimented on a sodium channel that is not coded by the SCN1A gene. Exhibit TT (report of Dr. Wiznitzer) and exhibit UU (report of Dr. Raymond). Dr. Kinsbourne did not present any disagreement with these views. See exhibit 73 (report of Dr. Kinsbourne, addressing exhibit TT and exhibit UU).

[26] Neurons contain different types of channels, including sodium channels, potassium channels, and calcium channels. See tr. 241 (Dr. Wiznitzer); tr. 376 (Dr. Kinsbourne); tr. 562 (Dr. Raymond).

make a general statement that the uncoupling of a modulator in an inhibitory neuron always leads to excitation is not the case." Tr. 516.[27]

d) National Childhood Encephalopathy Study

Thus far, the theory that the acellular pertussis vaccine can damage brain cells has been divided into three discrete propositions that have been examined on evidence that supports or contradicts the propositions made by Dr. Kinsbourne. See Moberly, 592 F.3d at 1325. Largely, these articles reported studies from laboratories, not studies on human beings. But, the record contains one study about human beings, the National Childhood Encephalopathy Study ("NCES").

The NCES is another basis for Dr. Kinsbourne's assertion that pertussis toxin affects neurons in humans. Tr. 20-21. The NCES reports the results of research into whether the whole-cell pertussis vaccine caused adverse neurological consequences. The NCES found that there was a greater incidence of acute neurological events within one month of the DTP vaccine. Tr. 21.[28] The NCES has been the basis for finding that the whole-cell version of the pertussis vaccine has caused a neurological injury. See Liable v. Sec'y of Health & Human Servs., No. 00-662V, 2000 WL 1517672 (Fed. Cl. Spec. Mstr. Sept 7, 2000).

Dr. Kinsbourne acknowledged that fewer reactions have been reported after the acellular pertussis vaccine compared to the whole-cell pertussis vaccine.

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[27] Mr. Harris asserts that Dr. Raymond agreed with the theory that "pertussis toxin uncouples the G-proteins and affects potassium channels." Pet'r Br. at 41 & n.17. This argument fails to recognize that Dr. Raymond said that pertussis toxin affects some (not all) G-proteins and the argument also indicates that Dr. Raymond testified about potassium channels when Dr. Raymond, in fact, did not testify about G-proteins affecting potassium channels.

[28] Whether the whole cell pertussis vaccine caused chronic (or permanent) neurological injury appears to be more disputed. Compare tr. 21-23 (testimony of Dr. Kinsbourne relying upon reports from the Institute of Medicine) with tr. 147-52 (testimony of Dr. Kinsbourne describing the reports from the IOM and also a report from the Committee on Infectious Diseases for the American Academy of Pediatrics) and tr. 269-77 (testimony of Dr. Wiznitzer).

According to Dr. Kinsbourne, only one-third as many reactions have been reported for acellular pertussis. Tr. 25, tr. 145-47; see also Saux.

Through Dr. Wiznitzer, respondent challenged Dr. Kinsbourne's reliance on studies of the whole-cell pertussis vaccine as a basis for conclusions about the acellular pertussis. Dr. Wiznitzer calculated that if the number of events reported after the whole-cell pertussis vaccine were reduced to one-third, then the incidence of neurologic events would approximately match the background rate. Tr. 238-41; tr. 278-82. Dr. Wiznitzer also relied upon a study by John B. Stephenson, who had access to raw data gathered by the NCES researchers because of his involvement in litigation in the United Kingdom. Tr. 231-36; tr. 334-36. Dr. Kinsbourne opined that no one suggests that the incidence rate for adverse events following acellular pertussis matches the background rate. Tr. 355. Dr. Kinsbourne also discounted the Stephenson study. Tr. 374.

Using studies about the whole-cell pertussis vaccine as a basis for conclusions about the acellular pertussis vaccine is problematic. Special masters have rejected this extrapolation in several cases. See Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at *10 n.15 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), motion for review granted on different ground and remanded, 95 Fed. Cl. 233 (2010); Teller v. Sec'y of Health & Human Servs., No. 06-804V, 2009 WL 255622, at *4 n.9 (Fed. Cl. Spec. Mstr. Jan. 13, 2009); Simon v. Sec'y of Health & Human Servs., No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1, 2007).[29]

Although these cases found that studies on the whole-cell pertussis vaccine did not constitute a reliable basis for making conclusions about the acellular

[29] Mr. Harris argues that he relies upon the NCES "to demonstrate, as a general proposition, and as the Federal Circuit has found, . . . that there is an increased risk of neurological symptoms in the post-pertussis vaccination period." Pet'r Br. at 43, citing Andreu, 560 F.3d at n.8. This citation to Andreu is misleading. Enrique Andreu, who was born in 1995, received the "diphtheria, whole-cell pertussis and tetanus ("DTP") vaccine." Andreu, 560 F.3d at 1371. Because Enrique received the DTP vaccine, whether the acellular pertussis vaccine causes the same effects as the whole cell pertussis vaccine was not before the Federal Circuit. Mr. Harris's argument based upon Andreu is no more persuasive than Dr. Kinsbourne's reliance on the NCES.

vaccine, reaching a similar conclusion here is not needed. As previously mentioned, even if Dr. Kinsbourne's theory that the DTaP vaccine can affect neurons were credited in full, Mr. Harris would not be entitled to compensation because the evidence clearly and convincingly establishes that Jordan's outcome would have been the same due to the SCN1A mutation.

Furthermore, respondent's challenge to the NCES, which is an epidemiological study, is based, in part, upon Dr. Wiznitzer's interpretation of incidence rates. Dr. Wiznitzer, like Dr. Kinsbourne, is a pediatric neurologist and Dr. Wiznitzer typically uses a statistician in his research. Tr. 328-29. Dr. Wiznitzer is not an epidemiologist, who would appear to be the most qualified person to interpret an epidemiological study.

In sum, on the topic of whether acellular pertussis vaccine can damage brain cells, there were shortcomings in the parties' presentations. Moreover, as set forth in section A, the evidence overwhelmingly favors a finding that the mutation in the SCN1A gene caused Jordan's epilepsy. These two reasons counsel against reaching any conclusion about the theory that acellular pertussis vaccine can cause an injury to a person's brain.[30]

2. DTaP, Fevers and Epilepsy

The theory that pertussis toxin impairs inhibitory neurons is not the only theory that Mr. Harris advances. At various places in his brief, Mr. Harris presents a different argument – that "[i]n Dr. Kinsbourne's view, the pertussis toxin in Jordan's DTaP vaccine caused the fever that caused seizure activity that led to severe epilepsy." Pet'r Br. at 40; accord id. at 17, 19, 24, 26.[31]

[30] To be sure, if resolving the issue were critical to the outcome, then the issue could be resolved based upon the existing record. See In re Claims, 2004 WL 1660351, at *8 (Fed. Cl. Spec. Mstr. July 16, 2004) (noting that "a factfinder in a legal case can always rule on a factual issue, even in the absence of any evidence") (emphasis in original). But, when this issue does not determine whether Mr. Harris is entitled to compensation, an exercise of judicial discretion tends to suggest deferring resolution of the issue until a case squarely presents the issue.

[31] Although Dr. Kinsbourne did present some testimony that the DTaP vaccine causes a fever, he also wrote that "[t]he mechanism by which the pertussis

A preponderance of evidence supports finding that DTaP vaccine can cause fevers and fevers can cause seizures. See tr. 49 (Dr. Kinsbourne); tr. 302 (Dr. Wiznitzer); tr. 348 (Dr. Wiznitzer stating that Jordan's "fever was a consequence of the vaccine"). Although establishing that vaccines can cause a fever and a fever can provoke a seizure assists Mr. Harris, Mr. Harris seeks compensation for more than just Jordan's first seizure. Mr. Harris attempts to link the first seizure to Jordan's "severe epilepsy." Pet'r Br. at 40. Thus, a critical question is whether DTaP, even if it caused Jordan's first seizure, affected Jordan's outcome?

A considerable amount of testimony focused on this issue. The evidence convincingly establishes that Jordan's first seizure did not affect his development. The primary evidence supporting this finding is research conducted by a team led by Dr. William A. Catterall. See tr. 316-17. Additional support comes from the testimony of Dr. Raymond and Dr. Wiznitzer, although their testimony rests, in some degree, on the work done by Dr. Catterall.

Dr. Catterall's team has conducted a series of experiments on the effects of mutations in the SCN1A gene. Tr. 455-56.[32] They use mice in which the murine equivalent of the SCN1A gene has been altered. (These mice are often known as "knock out mice" because the gene is sometimes entirely eliminated or "knocked out" from them but in other mice, the gene is partially removed. Tr. 456; see also tr. 42.) Persuasive evidence supports relying upon this animal model. Dr. Wiznitzer described this animal model as a "valid" model for the human condition. Tr. 317. Dr. Raymond said that the model was "excellent." Tr. 460. Dr.

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vaccine provokes the onset seizure is not by creating a non-specific fever." Exhibit 74 (Dr. Kinsbourne's supplemental report, dated July 6, 2010) at 2. This statement appears to be inconsistent with an assertion that "[i]n Dr. Kinsbourne's view, the pertussis toxin in Jordan's DTaP vaccine caused the fever." Pet'r Br. at 40.

[32] At the time of the hearing, the record contained only one article from the Catterall group and the lead author on that article was John C. Oakley. As discussed below, after the hearing, one additional article from the Catterall group, the Yu article, was filed into the record.

Catterall's group also characterized their mouse model for SMEI as "recapitulat[ing] the human disease with surprising fidelity." Oakley at 3998.[33]

Because the knock-out mice model is a paradigm for what happens to humans with SCN1A mutations, the mice can be the subject of an experiment to test Dr. Kinsbourne's hypothesis that a fever is needed to trigger a seizure. An experiment could be conducted in which knock-out mice are divided into two groups. In one group, mice are heated and in the other group, the mice are not heated. Then the outcome with respect to seizures could be measured. Dr. Kinsbourne stated that this experiment would be useful in this case. See tr. 43-46; tr. 165-69. Dr. Wiznitzer agreed that this experiment would show whether a fever was needed to trigger a seizure. Tr. 315.

This experiment was actually done and showed that knock-out mice will develop a seizure even if their temperature is not elevated. The first clue about this

[33] Dr. Kinsbourne's assessment of the animal model varied and the variance seemed to depend upon whether Dr. Kinsbourne thought that the Catterall experiment supported his opinion. In his direct testimony, Dr. Kinsbourne cited to the Oakley article and the mouse model. Tr. 43; tr. 88, tr 160-61. Dr. Kinsbourne stated that the mouse model was a "good one." Tr. 168. So, in his initial testimony, Dr. Kinsbourne accepted the mouse model.

After Dr. Kinsbourne testified, Dr. Wiznitzer asserted that the mouse model actually contradicts the theories offered by Dr. Kinsbourne. Tr. 306-07. In rebuttal, Dr. Kinsbourne argued that the mouse model was not valid. Dr. Kinsbourne stated that "the damage to the SCN[1]A gene was enormous in the knock-out mice. It was orders of magnitude greater than the kind of mutations that we're dealing with in the SMEI cases [of Jordan Harris and Nicholas Snyder]." To Dr. Kinsbourne, this distinction made any findings "not as definitive although one has to take note of it." Tr. 365; accord tr. 385.

Dr. Kinsbourne's claim that "orders of magnitude" separated what happens to knock-out mice from what happens in people was addressed by Dr. Raymond. Dr. Raymond explained that the mice had only one portion of gene eliminated, not the entire gene. Tr. 456; tr. 551-52. When Dr. Kinsbourne was asked about this point on rebuttal, he said that he would defer to Dr. Raymond on this point. Tr. 565-66. Thus, by a somewhat circuitous route, Dr. Kinsbourne also confirmed that the mouse model used by the Catterall group was a good model for what happens with humans.

experiment is found in a close reading of the Oakley article. Oakley stated that "We have previously reported spontaneous seizures in mSMEI [mice genetically programmed to develop a seizure disorder]" 21-27 days after birth. Oakley at 3996 (citing an article by FH Yu). In this context, "spontaneous" refers to developing a seizure in the absence of a rise in temperature. Dr. Wiznitzer explained that if the mice did not have seizures by day 21, then they "are going to develop spontaneous seizures in the next six days." Tr. 305.

In rebuttal testimony at the hearing, Dr. Kinsbourne was given an opportunity to address Oakley's report of "spontaneous seizures." In this context, Dr. Kinsbourne stated – inaccurately – that there were "orders of magnitude" of difference between the mice and people. Tr. 365. Dr. Kinsbourne did not state that the mice that had experienced "spontaneous seizures" actually were heated. See tr. 365.

In Dr. Raymond's testimony, he agreed with the testimony from Dr. Wiznitzer that the Catterall group of researchers have "just [left] the animals alone and they develop spontaneous seizures." Tr. 457. Dr. Raymond testified that "there's no need for any inflammatory, or infectious, or G-protein binding agents to do this model [cause seizures]. This model just does it on its own." Tr. 459. When called to testify in response to Dr. Raymond, Dr. Kinsbourne did not challenge Dr. Raymond's understanding of the Oakley article. See tr. 565-66.

Much of this evidence was summarized in respondent's brief filed after the hearing. Resp't Br. at 13-15. Mr. Harris also discussed the Oakley article in his brief, which was filed simultaneously with respondent's brief. Mr. Harris argued that "The Oakley article . . . does not indicate that mice with the SCN1A mutation will develop seizures without the influence of an environmental factor. . . . In this regard, it is significant that all rodents in the article had previously been heated to achieve a high core body temperature." Pet'r Br. at 37. Mr. Harris did not cite to any page in the Oakley article or to any testimony from an expert that established that "all rodents . . . had previously been heated." See id.

The parties' reply briefs, which were also filed simultaneously, continued to dispute the Oakley experiments. Respondent contended that Mr. Harris "offers no evidence to support his interpretation of the Oakley article, just the argument of his counsel." Resp't Reply at 6 n.4. Mr. Harris extended his argument. After quoting the portion of the Oakley article that cited to the article by Yu, Mr. Harris's reply

brief stated "it is clear that the mice in the earlier test had also been heated prior to experiencing later 'spontaneous' seizures. In other words, the term 'spontaneous' simply refers to the fact that the older mice, in both experiments, all of whom had initially been heated, subsequently experienced afebrile, or 'spontaneous' seizures." Pet'r Reply, filed July 19, 2010, at 16. Mr. Harris's citation to an "earlier test" implied that Mr. Harris's attorneys had learned details about an "earlier test" and the attorneys understood that the mice in the earlier test "had also been heated prior to experiencing later 'spontaneous' seizures." Id. Notably, when Mr. Harris's reply was filed, an article about the "earlier test" was not included in the record. The only testimony about additional tests conducted by the Catterall group came from Dr. Wiznitzer and Dr. Raymond, both of whom indicated that the mice experienced seizures without being heated. Tr. 307; tr. 316-17; tr. 457.

Given this divergent understanding of the experiments conducted by the Catterall group, an order was issued to solicit additional information from the parties. Respondent was ordered to supply, within 30 days, the article that supported Dr. Wiznitzer's assertion that the Catterall group had shown that knock-out mice experienced seizures without being heated. Respondent was permitted to provide any additional commentary from Dr. Wiznitzer or Dr. Raymond about any article. Mr. Harris was given an opportunity to file a response to support the claim from the reply brief (that in the earlier test, the mice that developed spontaneous seizures had been heated) and to address any information provided by respondent. Order, filed September 22, 2010.

Two days after the order was issued, respondent filed the Yu article. Respondent did not submit any additional testimony from Dr. Wiznitzer or Dr. Raymond because both doctors had discussed this article in their testimony. Respondent also maintained that the Yu article does not mention any heating of the mice. Respondent argued that Mr. Harris's "description of the article is inaccurate." Resp't Notice of Filing, dated Sept. 24, 2010, at 1.

A response from Mr. Harris was expected within 30 days as set in the September 22, 2010 order. No response was filed within this time. After the deadline had passed, another order was issued to allow Mr. Harris a second opportunity to substantiate the assertions made by his attorney in the reply brief. Order filed, Nov. 23, 2010.

Mr. Harris complied with the second order and discussed the experiment reported by Yu. Mr. Harris's response correctly indicates that the researchers surgically implanted electrodes into mice. Pet'r Resp., filed Dec. 17, 2010, at 2, citing Yu at 1148. Mr. Harris then asserts that "As part of the normal healing process from surgery, it is not unusual for there to be temperature elevation. Thus, the heating in this case was not extrinsically applied as in the Oakley article, . . . but would reflect an intrinsic elevation in core body temperature secondary to the healing process." Id.

Mr. Harris's interpretation of the Yu article is strained. Mr. Harris's argument, which was produced only after two orders, rests upon an assertion that mice will have a fever after surgery. Mr. Harris gives any post-surgery fever much more importance than the Yu researchers did because they did not report any temperature measurements after the surgery. Mr. Harris's argument is not persuasive.

Mr. Harris has 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. Mr. Harris could have submitted evidence in the form of a supplemental report from Dr. Kinsbourne. Yet, even after these opportunities, Mr. Harris has not presented any persuasive argument to distinguish these studies. It is very likely that Dr. Wiznitzer's understanding of these experiments is accurate. The Catterall researchers showed that mice with a mutation to the gene that codes a sodium channel will have seizures regardless of whether the mice are heated. Due to reliability of the mouse model, this finding may be transferred to humans who have a genetic mutation. Humans with a genetic mutation do not need to have a fever to have a seizure.

The experience with humans confirms that a fever is not necessary to trigger seizures. Although the first seizure in many cases of SMEI is a seizure associated with a fever, all cases of SMEI do not start that way. Tr. 60; tr. 107; tr. 110; tr. 120; tr. 252; Ceulemans (2004b) at 96. As Dr. Kinsbourne explained in a report filed after the hearing: "the presence or absence of fever is immaterial to the provocation of the onset of seizure." Exhibit 74 (report, dated July 19, 2010) at 2.

In sum, based upon all the evidence in the record and for all the reasons listed above, Jordan's SCN1A mutation was the sole cause of his epilepsy. The DTaP vaccine triggered a fever and the fever triggered a seizure. But, Jordan

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 Jordan's development.

V. Analysis -- Six Month Requirement

An alternative method for analyzing Jordan's case is to examine whether Mr. Harris has established that Jordan suffered an injury that lasted more than six months. Even when a vaccine adversely affects the recipient, compensation may be awarded only when the injury has some degree of severity. This element can be met by establishing any of three alternatives specified in the statute and, in this case, the only one that is potentially applicable is that the person "suffered the residual effects or complications of such illness, disability, injury or condition for more than 6 months after the administration of the vaccine." 42 U.S.C. § 300aa–11(c)(1)(D). The burden of establishing six-months of harm falls to petitioners.[34] Song v. Sec'y of Health & Human Servs., 31 Fed. Cl. 61, 65-66 (1994), aff'd, 41 F.3d 1520 (Fed. Cir. 1994) (table).

The evidence here convincingly demonstrates that the DTaP vaccination did not affect Jordan's development. It is Dr. Kinsbourne's opinion that Jordan's genetic mutation was not the sole cause of Jordan's condition, and that the pertussis vaccine "substantially contributed" to Jordan's development. Tr. 86-87. That much is clear. However, Dr. Kinsbourne did not offer any ideas of how Jordan would have been "but for" the vaccine. For example, when asked whether the seizure disorders in these cases would not have been manifest "absent the receipt of the DTaP" vaccine, Dr. Kinsbourne testified that he has "no knowledge of that. That would be speculation." Tr. 118. When asked to explain how Jordan would have been different today if he had not received the vaccine, Dr. Kinsbourne stated that he did not know. Tr. 172. Later at the end of the hearing, Dr. Kinsbourne testified that "it might be that if he [Jordan] had not had this

[34] In his reply brief, Mr. Harris argues that in the circumstances of his case, "it is respondent's burden to show that any vaccine-related injury did not last six (6) months." Pet'r Reply at 12-13. This argument, which was made without citation to any cases, is in conflict with other authorities. Arguments regarding the burden of proof are not material because, as explained with regard to the question of causation, this case turns on the evidence, not legal doctrines.

vaccination that he would have had a milder form of the condition or no form of the condition. I don't know." Tr. 582.

Even in a supplemental report after the hearing, Dr. Kinsbourne did not present evidence that Jordan would have been different "but for" his vaccination. After the hearing, respondent presented the recently published McIntosh article that had concluded that the clinical outcome for children with an SCN1A-related disorder did not vary as to whether the child had a seizure within two days of vaccination. In Dr. Kinsbourne's response to McIntosh, Dr. Kinsbourne stated "I have never argued that they [children who had a seizure within two days of receiving a pertussis vaccine] do so differ [from children who did not have a seizure after receiving a pertussis vaccine], and that has never been the issue." Exhibit 74 at 2. Dr. Kinsbourne's assessment misses the point entirely. Mr. Harris's case is based upon an assertion that Jordan is worse (different) because of the vaccine. Contrary to Dr. Kinsbourne's statement, this difference (or the lack thereof) has always been an issue. In trying to determine whether Jordan is different, Dr. Kinsbourne adds relatively little when he states that "People who sustain SMEI after being vaccinated might have become subject to one of the less devastating conditions on the spectrum had they not been provoked into SMEI by the vaccination." Id. This statement is inherently speculative and overlooks the fact that Jordan does not have SMEI. Jordan has a less devastating condition.

The uncertainty about Jordan's outcome but for the vaccination that is inherent in Dr. Kinsbourne's testimony is not present in the testimony of Dr. Wiznitzer and Dr. Raymond. Both of these doctors testified that the vaccines did not cause Jordan's epilepsy. Tr. 223 (Dr. Wiznitzer stating that the vaccines played no role in causing Jordan's epilepsy); tr. 226 (Dr. Wiznitzer stating "we know that there's a causal association between the mutation and this type of fever-related epilepsy"); tr. 346 (Dr. Wiznitzer stating that the McIntosh study from Australia showed that "there's no alteration of the natural history" of the condition); tr. 349-50 (Dr. Wiznitzer stating "knowing the natural history of this disorder, you don't need . . . the vaccination administration to end up the same way."); tr. 455 (Dr. Raymond stating that the DTaP vaccination "had no role in his presentation, his mutation, or his subsequent course" and the genetic mutation has "sufficient causality to explain all of [Jordan's] subsequent course"); tr. 474 (Dr. Raymond stating "no[]where in the literature have I found that environmental factor plays out in the ultimate expression of this condition"); tr. 523 (Dr. Raymond stating "the lack of protein [created by the SCN1A gene] results in a

condition we refer to as Dravet's Syndrome. . . . [I]t doesn't make a difference whether I have Dr. Kinsbourne's excitotoxicity."); tr. 546 (Dr. Raymond stating that a majority of pediatric neurologists would say "it's sufficient causality to have the mutation"). This testimony is compelling evidence that the vaccine did not affect Jordan's ultimate outcome.

Furthermore, the evidence also fails to indicate any consequences of the fever that Jordan experienced immediately after the vaccine lasted more than six months. This fever triggered Jordan's first seizure. The first seizure lasted five to ten minutes and can be categorized as a "complex seizure" because it was focal (on his left side). Tr. 58; tr. 112-13; tr. 322.

The experts did not assert that the fever, by itself, had any lasting consequences. For example, Dr. Kinsbourne did not have the opinion that relatively early onset of seizures (approximately two months old), made Jordan's condition more severe. Tr. 153-54. Dr. Kinsbourne could not say if the fever that Jordan experienced after his vaccination was necessary to trigger his seizure disorder. In this context, Dr. Kinsbourne stated that "if he [referring to Nicholas Snyder, the child in the other case involving SCN1A] had had no fevers in his infancy, I [Dr. Kinsbourne] have no idea whether he would have developed the illness anyway." Tr. 108.

Respondent's experts were more emphatic. Dr. Wiznitzer stated that fever "doesn't alter the natural history of the condition but it just provokes a seizure." Tr. 237; accord tr. 306. Later, relying on the McIntosh study from Australia, Dr. Wiznitzer stated that outcome of children with a genetic epilepsy did not vary regarding whether a fever triggered their first seizure. Tr. 256-57.[35] Dr. Raymond stated that based upon the Oakley article, the length and type of seizure does not affect the outcome. Tr. 460. Dr. Raymond also rejected the idea that the first seizure lowers the seizure threshold so that more seizures are likely. Tr. 518-19.[36]

[35] Although the McIntosh article had not been published when the hearing was held, the McIntosh article did corroborate Dr. Wiznitzer's statement.

[36] Special masters have awarded compensation when petitioners established that a child had a complex febrile seizure within a few days of a vaccine and that child developed epilepsy. E.g. Mersburgh v. Sec'y of Health & Human Servs., No. 04-997, 2007 WL 5160384 (Fed. Cl. Spec. Mstr. July 9, 2007); Simon v. Sec'y of Health & Human Servs., No. 05-941V, 2007 WL 1772062 (Fed. Cl. Spec. Mstr.

For these reasons, the evidence does not show that the DTaP vaccine affected Jordan's epilepsy for more than six months. Instead, the evidence is much more consistent with a finding that Jordan's ultimate outcome was the same as it would have been but for the vaccine. The finding that any problems did not last for more than six months derives from the finding that the genetic mutation was the sole cause of Jordan's epilepsy. If the genetic mutation was the sole cause, then, simply as a matter of logic, the vaccine did not alter Jordan's development.

The lack of evidence that the vaccine caused Jordan to suffer any problems for more than six months makes this case comparable to other cases in which petitioners have been found not entitled to compensation for failing to meet the six-month requirement found in section 11(c)(1)(D). See Starvridis v. Sec'y of Health & Human Servs., No. 07-261V, 2009 WL 3837479, at *4 (Fed. Cl. Spec. Mstr. Oct. 29, 2009) (stating "petitioner was either unable or unwilling to produce an opinion from a treating physician or medical expert opining that William's alleged injury persisted subclinically beyond six months" and denying compensation to petitioner); Song v. Sec'y of Health & Human Servs., No. 92-279, 1993 WL 534746 (Fed. Cl. Spec. Mstr. Dec. 15, 1993), aff'd, 31 Fed. Cl. 61 (1994), aff'd, 41

June 1, 2007); Cusati v. Sec'y of Health & Human Servs., No. 05-5049V, 2005 WL 4983872 (Fed. Cl. Spec. Mstr. Mar. 9, 2006). Those decisions are based upon different facts.

One prominent difference is that Jordan is known to have an SCN1A mutation. The children in the other cases do not. See Mersburgh, 2007 WL 5160384, at *3 (stating "the record is devoid of evidence of a genetic predisposition to epilepsy"); Simon, 2007 WL 1772062, at *2 (noting that a "DNA analysis was never performed on Devin"). Cusati did not discuss DNA testing but notes that respondent failed to identify an alternative cause for the seizures. Cusati, 2005 WL 4983872, at *11.

Another difference is that Jordan's seizure, although a febrile seizure, did not last very long. Two of the three other children had much more severe seizures. Cf. Mersburgh, 2007 WL 5160384, at *2 (Elijah's seizure lasted at least 47 minutes and was diagnosed as status epilepticus); Simon, 2007 WL 1772062, at *3 (Devin's initial seizure lasted for 50 minutes). The third child had successive seizures. Cusati, 2005 WL 4983872, at *3 (noting that the "episode lasted four minutes" and a second episode "lasted three minutes") and at *7 (summarizing expert's testimony that Eric had a "complex" seizure because he had two events within 24 hours).

F.3d 1520 (Fed. Cir. 1994) (table). The lack of evidence showing that Jordan suffered an injury for more than six months is another reason that Mr. Harris is not entitled to compensation.

VI. Conclusion

The evidence overwhelmingly favors a finding that Jordan's epilepsy was caused solely by a mutation in the SCN1A gene. Respondent's experts, Dr. Wiznitzer and Dr. Raymond, testified consistently and in accord with relevant medical articles. Their opinions in this litigation matched how they counsel patients with genetic-based neurological disorders.

To the extent that Mr. Harris relied upon medical articles discussing the SCN1A gene, Mr. Harris repeatedly misunderstood the articles. For some articles, such as Berkovic and Claes, Mr. Harris's briefs make sweeping statements that exaggerate the articles' findings or overlook qualifications in the articles themselves. For the Oakley and Yu articles, Mr. Harris's arguments appear manufactured.

Mr. Harris's reliance on Dr. Kinsbourne's testimony is similarly unsound. Dr. Kinsbourne brought very little helpful information. Sometimes, 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. Dr. Kinsbourne made assertions that he was forced to modify or to retract. The inconsistencies in Dr. Kinsbourne's testimony severely undermined his credibility.[37]

Because the evidence shows that Jordan's epilepsy was caused by the genetic mutation, Mr. Harris is not entitled to compensation. The Clerk's Office is

[37] Some of these concerns may be addressed if Mr. Harris seeks an award of attorneys' fees and costs. See Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 3790297, at *5-9 (Fed. Cl. Spec. Mstr. Sept. 9, 2010) (reducing Dr. Kinsbourne's hourly rate and reducing the number of hours for Dr. Kinsbourne's work).

directed to enter judgment in accord with this decision unless a motion for review is filed.

IT IS SO ORDERED.

s/ Christian J. Moran
Christian J. Moran
Special Master

Appendix – Citations to Medical Literature

Author	Citation	Harris	Snyder
Berkovic	Samuel F. Berkovic et al., "De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study", 5 Lancet Neurol 465 (2006)).	A, 26	E
Burgess	DL Burgess, "Neonatal epilepsy syndromes and GEFS+: Mechanistic considerations", 46 Epilepsia (Suppl 10) 51 (2005)).	27	38
Catterall	William A. Catterall, "Inherited neuronal ion channelopathies: new windows on complex neurological diseases" (Chapter 27) in Jasper's Basic Mechanism of Epilepsies (A.V. Delgado Escueta et al. eds. (1999)).	59	89
Ceulemans, A	Berten P.G.M. Ceulemans et al., "Clinical correlations of mutations in the SCN1A gene: From febrile seizures to severe myoclonic epilepsy in infancy", 30 Pediatr. Neurol. 236 (2004)) at 237.	29	40
Ceulemans, B	Berten Ceulemans and Patrick Cras, "Severe Myoclonic Epilepsy in Infancy", 104 Acta Neurol. Belg. 95 (2004)).	H	41
Claes, A	Lieve Claes et al., "De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy", 68 Am. J. Hum. Genet. 1327.	LL	G
Claes, B	Lieve RF Claes et al., "The SCN1A Variant Database: A Novel Research and Diagnostic Tool", 30 Hum. Variation E904 (2009) online at E906.	KK	FF
Claes, C	L Claes et al., "De novo SCN1A mutations are a major cause of severe myoclonic epilepsy of infancy," 21(6) Hum. Mutation 615 (2003).	G	F
Corbel	Michael J. Corbel & Dorothy K. L. Xing, "Toxicity and potency evaluation of pertussis vaccines", 3(1) Expert Rev. Vaccines 89 (2004)).	60	90
Cyr	Terry Cyr et al., "A quantitative analysis for ADP-ribosylation activity of pertussis toxin: an enzymatic-HPLC coupled assay applicable to formulated whole cell and acellular pertussis vaccine products", 29 Biologicals 81 (2001)).	61	91
Depienne	Christel Depienne et al., "Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients", ___ J. Med. Genet. ___ (2008)).	56	83
Gambardella	Antonio Gambardella and Carla Marini, "Clinical spectrum of SCN1A mutations", 50 Epilepsia 20 (2009)).	54	81

Author	Citation	Harris	Snyder
Gomez	S.R. Gomez et al., "ADP-ribosylation Activity in Pertussis Vaccines and its Relationship to the in vivo Histamine-Sensitisation Test", 25 Vaccine 3311 (2007)).	66	95
Kimura	K Kimura et al., "A missense mutation in SCN1A in brothers with severe myoclonic epilepsy in infancy (SMEI) inherited from a father with febrile seizures", 27 Brain Dev 424 (2005)).	36, NN	48, M
Kumakura	Akira Kumakura et al., "Novel de novo splice-site mutation of SCN1A in a patient with partial epilepsy with febrile seizures plus", 31 Brain & Development 179 (2009)).	JJ	NN
Lossin	Christoph Lossin, "A Catalog of SCN1A Variants", ___ Brain & Development ___ (2008)) at 3.[38]	55	82
McIntosh	Anne M. McIntosh, et al., "Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study", 10 Lancet Neurol 1 (2010)).	VV	99, Tab A
Morimoto	Masafumi Morimoto et al., "SCN1A Mutation Mosaicism in a Family with Severe Myoclonic Epilepsy in Infancy", 47 Epilepsia 1732 (2006)).	N	P
Mulley	John C. Mulley et al., "SCN1A Mutations and Epilepsy", 25 Human Mutation 534 (2005)).	38	52, Q
Nieto-Barrera	J. Nieto-Barrera et al., "Severe myoclonic epilepsy in childhood. Epidemiologic analytic study", 30(7) Rev Neurol 620 (2000)).	40	54
Oakley	John C. Oakley et al., "Temperature-and-age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy", 106(10) PNAS 3994 (2009)).	AA	CC
Ohmori	I. Ohmori et al., "Significant correlation of the SCN1A mutations and severe myoclonic epilepsy in infancy," 295(1) Biochemical & Biphysical Res. Comm. 17 (2002).	Resp. Trial Ex. 1	Resp. Trial Ex. 1
Rhodes	Rhodes TH et al., "Nonactivating voltage-gated sodium channels in severe myoclonic epilepsy of infancy", 101 PNAS 11147 (2004)).	42	56

[38] The record contains the "article in press" version of the article by Lossin. Thus, volume and page numbers are not available.

Author	Citation	Harris	Snyder
Saux	Nicole Le Saux et al., "Decrease in Hospital Admissions for Febrile Seizures and Reports of Hypotonic-Hyporesponsive Episodes Presenting to Hospital Emergency Departments Since Switching to Acellular Pertussis Vaccine in Canada: A Report From IMPACT", 112 Pediatrics 348 (2003)).	OO	Z
Sell	Erick Sell and Berge Minassian, "Demystifying vaccination-associated encephalopathy", 5 Lancet Neurol 465 (2006)).	43	57
Stephenson	John B. Stephenson, "A Neurologist Looks at Neurological Disease Temporally Related to DTP Immunization", 13 Tokai J. Exp. Clin. Med. 157 (1988)).	R	U
Thalmann	Robert H. Thalmann, "Evidence that guanosine triphosphate (GPT)-binding proteins control a synaptic response in brain: effect of pertussis toxin and GTPyS on the late inhibitory postsynaptic potential of hippocampal CA3 neurons", 8 J. Neuroscience 4589 (1988)).	64	94
Turnbull	Julie Turnbull et al., "Sacred disease secrets revealed: the genetics of human epilepsy", 14 Human Molecular Genetics 2491 (2005)) at 2492.	44	60
Wallace	RobynWallace, "A plethora of SCN1A mutations: What can they tell us?", 5 Epilepsy Currents 17 (2005)).	45	61
Yakoub	Moncef Yakoub et al., "Early diagnosis of severe myoclonic epilepsy in infancy", 14 Brain Dev 299 (1992)).	46	62, V
Yu	Frank W. Yu et al., "Reduced sodium current in GAGAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy", 9 No. 9 Nature Neuroscience 1142 (2006)).	WW, 65	WW, 96