In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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TRYSTAN SANCHEZ, by and through his parents, GERMAIN SANCHEZ and JENNIFER SANCHEZ,	*	No. 11-685V
	*	Special Master Christian J. Moran
	*	Filed: October 9, 2018
Petitioners,	*	
v.	*	Entitlement; DTaP; Leigh's syndrome; mitochondrial disorder; decompensation; genetic mutation; SDHA.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *		

Lisa A. Roquemore, Law Offices of Lisa A. Roquemore, Rancho Santa Margarita, CA, for petitioners;
Jennifer L. Reynaud, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Germain and Jennifer Sanchez bring this action on behalf of their son, Trystan, claiming that his mitochondrial disease, known as Leigh's syndrome, was

[1] Because this decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). This means the decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material before posting the decision.

caused or significantly aggravated by his six-month vaccinations. The parties agree that Leigh's syndrome is a genetic disorder caused, at least in part, by inherited mutations in Trystan's DNA. However, the Sanchezes argue that Trystan's disease would not have been expressed but for his vaccination or, alternatively, that the course of his disease was significantly worse than it would have been but for the vaccination. While the Sanchezes sufficiently demonstrate that vaccines could contribute to the manifestation of Leigh's syndrome, the evidence does not indicate that this is what happened to Trystan. Accordingly, the Sanchezes are not entitled to compensation.

I. Facts

The parties hold two very different accounts of Trystan's health in the months following the administration of his six-month vaccinations on February 5, 2009. To address this discrepancy, the undersigned held a fact hearing to take testimony from the Sanchez family in May 2012, and issued a ruling finding facts on April 10, 2013. For the purposes of this decision, the period in which the parties hold divergent viewpoints about Trystan's health is segregated from the rest of the factual history.

A. Trystan's Early Life and the February 5, 2009 Vaccinations

Trystan was born on August 16, 2008, to Jennifer and Germain Sanchez. Exhibit 1 at 89. At birth, Trystan appeared to be a normal, healthy child. Id. at 89. Trystan and his mother were discharged on August 18, 2008. Id. at 106.

Four days later, on August 22, 2008, Trystan was seen by his pediatrician for a check-up and to be circumcised. The pediatrician observed that Trystan was jaundiced, but otherwise the physical exam appeared to be normal. Id. at 34-35. During this visit, Trystan received his first dose of the hepatitis B vaccine. Id. at 35-38. No adverse response is noted in the medical records. One week later, on August 29, 2008, Trystan returned for some routine follow-up care from the circumcision. Id. at 40. He did not return to the pediatrician again until he was nearly six-months old. Id. at 44.

The Sanchezes testified that Trystan appeared healthy during his first six months. Tr. 62. During that time, he would smile, laugh, play, and babble. Tr. 16-17, 27, 41, 50, 62-63, 110, 147-49, 176-77. He was also making eye contact, did not cry that much, and began trying to crawl. Tr. 16-17, 41, 63, 148. He was able to roll over, hold his bottle and sippy cup, and play peekaboo. Tr. 16, 50-51, 62, 110, 148, 176. Given that Trystan appeared so healthy, his parents did not take

him to the doctor in his first six months following the follow-up visit from his circumcision. Tr. 62, 177.

Trystan was taken to his six-month well-baby checkup with Dr. Philip Brown on February 5, 2009. Exhibit 1 at 44. Dr. Brown found his growth and development to be normal. Id. at 46. Dr. Brown noted that Trystan was meeting his developmental milestones, including: turning to sound, self-feeding, self-comforting, responding to his name, sitting with support, grasping and mouthing objects, smiling, laughing, squealing, showing interest in toys, showing differential recognition of parents, babbling reciprocally, rolling over from back to front, and standing when placed. Trystan also had "no head lag when pulled to sit." Id. On this day, he received the diphtheria-tetanus-pertussis (DTaP), hepatitis B, Haemophilus influenzae type B (Hib), and pneumococcal conjugate (PCV) vaccines. Id. Dr. Brown recommended that Trystan return in two months to receive further vaccinations. Id.

The Sanchezes testified that Trystan had an adverse reaction to the vaccinations he received on February 5, 2009. They noted that after the wellness check with Dr. Brown, Trystan was inconsolable; he cried a loud, high-pitched cry, as if he was in pain. Tr. 18-19, 67, 177-79. He began to run a temperature of 102.2 degrees and developed a lump on his left thigh that was "really hot." Tr. 17-20, 32, 67-69, 113, 177-79. Mrs. Sanchez gave Trystan Tylenol for the fever, which ebbed and flowed over the next few days. Tr. 20, 30, 68, 151, 178, 180. The Secretary did not contest that Trystan experienced fever following vaccination. See Joint Statement at 4, ¶ 11.

B. Controverted Aspects of Trystan's Medical History

The parties hold significant disagreements about Trystan's health in the months following the February 5, 2009 vaccination. The crux of the disagreement between the parties relates to how much weight the undersigned should give to oral testimony when that testimony is in conflict with documents created contemporaneously with the events that they are describing. More specifically, Trystan's medical records indicate that in the period following the administration of his vaccinations in February 2009, Trystan suffered from colds but was neurologically normal. However, members of Trystan's family recall otherwise. In the ruling finding facts, the undersigned largely credited the contemporaneous medical records.

Though Trystan's medical records and the testimony provided by his family members are thoroughly reviewed in the ruling finding facts, both are briefly revisited and summarized here for the purpose of this decision. In reviewing the

factual history for this period, this decision divides the evidence that arises out of the medical records from the evidence that comes from the testimony provided by Trystan's family.

1. Medical Records

On the morning of February 17, 2009, Trystan returned to the pediatrician for an urgent care visit during which he was examined and treated by Physician Assistant Jonathan P. Luna. Mr. Luna diagnosed Trystan with a "[c]ommon cold" and "[v]iral syndrome." Exhibit 1 at 48. Trystan's temperature was 98.9 degrees and "fever" was noted. Id. at 49. Mrs. Sanchez told Mr. Luna that Trystan had been coughing and congested with fever. Id. at 49. The records do not indicate that Mrs. Sanchez told Mr. Luna anything about Trystan exhibiting unusual arm movements or other signs of a neurological condition. See id. at 48-51.

That next visit to the pediatrician occurred on April 29, 2009 (nearly three months after the vaccination), when Trystan was seen by Dr. Nabil R. Seleem. Id. at 50. The medical records note that Trystan had suffered cough and congestion for two weeks prior to the visit. Id. However, no unusual arm movements or developmental issues were reported. The records indicate that Dr. Seleem performed a neurological review and further stated that he identified "no neurological symptoms." Ultimately, he diagnosed Trystan with an ear infection and bronchitis and prescribed amoxicillin. Id. at 50-52.

Trystan returned to the clinic two weeks later to see Dr. Brown on May 13, 2009. Dr. Brown observed that Trystan's symptoms appeared to be resolving, and he recommended continued use of a humidifier. No reports of loss of skills were made, or observed, at this time. Id. at 53.

At one year old, Trystan was seen by Physician Assistant Micaela Marin-Tucker for a well-child exam. Exhibit 1 at 54-56. Mrs. Sanchez informed Ms. Marin-Tucker that she "noticed a change in [Trystan's] development about 2-3 months ago [the May-June time period] but since she had taken [Trystan to the pediatric clinic] with Dr. Brown she thought that everything was ok." Exhibit 1 at 54. Upon a review of systems, Ms. Marin-Tucker found that Trystan did not walk, stand, crawl, hold his head up while sitting, or make any attempt to move his lower extremities. She also noted in her examination that his extremities seemed soft, yet rigid at times. As the result of her examination, Ms. Marin-Tucker ordered a battery of lab tests. Id. at 54-55. She also referred Trystan to a neurologist, physical therapist, and occupational therapist. Id. at 55. Additionally, Trystan received his third hepatitis B vaccine, as well as his second doses of the pneumococcal conjugate, DTaP, and Hib vaccines. Id. at 55. Trystan was to

return to the nurse the next week to receive the remaining vaccinations that were due, including the measles-mumps-rubella, varicella, and hepatitis A vaccines. Id. at 55.

2. Testimony

Mr. Sanchez testified that Trystan began exhibiting unusual arm contortions on the night of February 16, 2009, a day after his wife's birthday, and 11 days after Trystan's vaccinations. Joint Statement of Uncontroverted Facts [hereinafter Joint Statement], filed Nov. 8, 2012, at 4-5, ¶ 13; Tr. 184-86. Mrs. Sanchez testified that, during an urgent care visit to the pediatrician the following day (February 17, 2009), she informed Physician Assistant Jonathan P. Luna that Trystan had been coughing, congested, and febrile. Joint Statement at 5, ¶ 15; Tr. 74-75, 115. She also testified that she told Mr. Luna of Trystan's arm movements, but that he did not seem concerned and did not note her concerns. Joint Statement at 5, ¶ 15 n.4; Tr. 74-75, 115.

The Sanchezes testified that Trystan exhibited arm contortion, rigidity, and inconsolable crying in March 2009. Joint Statement at 5-6, ¶ 16; Tr. 25, 43, 79, 135-36, 191, 219-20. Additionally, Mrs. Sanchez testified that, between her birthday and late April 2009, when she next took Trystan to the doctor, Trystan lost head and trunk control, no longer made eye contact, did not want to play, and continued to have arm contortions. Joint Statement at 6, ¶ 17; Tr. 76, 78, 111-12. According to Mrs. Sanchez, she did not return to the doctor until late April because she had been told by the physician assistant that Trystan was fine. Joint Statement at 6, ¶ 17; Tr. 75-77, 83, 134.

Regarding the April 29, 2009 visit with Dr. Seleem, Mrs. Sanchez testified that, although she told Dr. Seleem about Trystan's arm movements, he did not note her concerns. Tr. 80, 116, 125. And, despite the indication in the medical records that Dr. Seleem conducted a neurological exam, Mrs. Sanchez testified, based on her observation of later neurological exams, that he did not perform a neurological exam. Joint Statement at 7, ¶ 18 n.8; Tr. 80-81, 136-37.

As for the May 13, 2009 visit with Dr. Brown, Mrs. Sanchez and her mother testified that Dr. Brown was not listening, was unresponsive to the issues being brought up, and was very rude and hurried. Joint Statement at 7, ¶ 19 n.10; Tr. 85-87, 156-58.

In summation, Mr. and Mrs. Sanchez and their close relatives testified that they noticed Trystan getting "sick all the time" in the six months after his February 5, 2009 vaccinations. Joint Statement at 8, ¶ 20; Tr. 20, 33, 36, 70, 164-65, 181. They also stated that Trystan began to lose skills during the same six-month period. Joint Statement at 8, ¶ 20; Tr. 21-23, 33, 86, 190. According to their testimony, Trystan could no longer roll, crawl, sit, hold his bottle, make eye contact, or try to talk. He was silent, detached, and lost the ability to control his head, sit, stand, talk, eat and chew. Joint Statement at 8, ¶ 20 n.12; Tr. 21-23, 33, 86, 190.

3. Findings of Fact

The findings of fact and the rationale for those findings are provided in the April 10, 2013 Ruling Finding Facts. However, the contents of this ruling are briefly reviewed here.

Broadly speaking, the undersigned declined to favor the recollections provided by the Sanchez family over the contemporaneously recorded medical records as they related to Trystan's condition following the receipt of the vaccine on February 5, 2009. The relative weight that the undersigned gave to the contemporaneously created medical records is consistent with the guidance provided to fact-finders by the United States Supreme Court and the Federal Circuit. See Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993) (citing United States v. Gypsum, 333 U.S. 364, 396 (1947)). Ultimately, the undersigned found that the most likely explanation for the disparity between the medical records and the Sanchezes' recollections was that the Sanchezes' recall of events was limited by the passage of time. The undersigned did not doubt the sincerity of the Sanchezes' beliefs and recognizes that the Sanchezes may very well be correct in their recollections.

The undersigned recognizes that the Sanchezes have highlighted subsequent medical records that place the onset of Trystan's loss of skills at six months of age. For example, the Sanchezes submitted an EEG report from September 17, 2010, which reflects a parental report that Trystan had been "having jerking movements at six months of age." Exhibit 1 at 181; Joint Statement at 12, ¶ 35 n.15. In addition, Dr. Haas stated that Trystan's symptoms occurred "following [the February 5] vaccination" and "repeated with the next set of vaccines at 12 months." Exhibit 52 at 1-2. However, each of these physicians based their histories on the parents' subsequent narrative of events, wherein the onset of Trystan's neurological disorder occurred in proximity to the vaccines. The subsequent narratives, though documented in medical records, cannot be given the same weight as the contemporaneously created records. See Castaldi v. Sec'y of

Health & Human Servs., No. 09-300V, 2014 WL 3749749, at *11 (Fed. Cl. Spec. Mstr. June 25, 2014) ("the records of treating physicians can be questioned and the weight afforded to them depends on whether the physician is noting her own observations or merely recording statements made by the patient"), mot. for rev. denied, 119 Fed. Cl. 407 (2014). Cf. Dobrydnev v. Sec'y of Health & Human Servs., 566 F. App'x 976, 983 (Fed. Cir. 2014) (a special master may refrain from crediting the finding of a doctor who obtained an inaccurate history).[2]

The undersigned is tasked with weighing the evidence and finding those facts that are, more likely than not, true. Despite the Sanchezes' sincere recollections of events, the undersigned found that the contemporaneous medical records spoke louder. Thus, for the purposes of this decision, the undersigned finds that following facts to be, more likely than not, true:

- In the hours following the vaccination, Trystan developed a fever and displayed inconsolable crying. This fever ebbed and flowed for a few days.

- Ten days after the vaccination, on February 15, 2009, Trystan developed another fever and was crying inconsolably again. Trystan was congested and had difficulty breathing. His arms contorted and he was jerking around. However, these movements were of the type typically displayed by an infant suffering from a cold.

- Trystan's family did not convey to Physician Assistant Luna, during the February 17, 2009 visit, that Trystan had displayed any symptoms consistent with a neurological injury as opposed to a cold.

- During the February 17, 2009 visit with Mr. Luna, Trystan did not display any signs upon examination that were consistent with a neurological injury as opposed to a cold.

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[2] Similarly, before Dr. Haas diagnosed Trystan as suffering from Leigh's syndrome, other doctors associated Trystan's condition, as they understood it, with a vaccination. But, these records carry little weight as they are based upon incomplete and/or incorrect information.

- Between the February 17, 2009 visit with Mr. Luna and the April 29, 2009 visit with Dr. Seleem, Trystan did not have any symptoms that were inconsistent with a cold.

- Trystan was brought to see Dr. Seleem on April 29, 2009, because his parents were concerned about his cough and congestion that had lasted for two weeks.

- Trystan's family did not convey to Dr. Seleem, during the April 29, 2009 visit, that Trystan had displayed any symptoms consistent with a neurological injury as opposed to a cold.

- Dr. Seleem did not observe any signs consistent with a neurological injury during the examination performed on Trystan during the April 29, 2009 visit. Instead, Trystan had a cold.

- The undersigned credits the report provided by Trystan's mother to Physician Assistant Marin-Tucker on August 17, 2009, regarding the timeline of when Trystan first started showing signs of loss of skills. Trystan's mother reported that the onset was approximately 2-3 months prior to the August 17, 2009 visit and also associated the timing with the visit with Dr. Brown on May 17, 2009. Thus, the undersigned finds it likely that the first signs of Trystan's loss of skills occurred in the beginning of May 2009, at the earliest.[3]

See Ruling Finding Facts, issued Apr. 10, 2013, at 11-16.

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[3] In the Ruling Finding Facts, the undersigned set a broad range of May 17, 2009 to June 17, 2009, as being the likely timeframe for when Trystan started showing loss of skills. This timeframe relied on the 2-3 month range provided by Ms. Sanchez during the August 17, 2009 appointment, and not the note that Trystan's loss of skills were raised during the visit to Dr. Brown on May 17, 2009. The medical records show that Trystan's loss of skills did not precipitate the visit to Dr. Brown (a cold did), but it is conceivable that Ms. Sanchez raised the concern and Dr. Brown dismissed the concern without making a record of it because the loss of skills had been mild by that point. Regardless, the evidence does not favor that Trystan's loss of skills developed before May 2009.

C. Uncontroverted Facts Following August 17, 2009 Visit

About six weeks later, on October 7, 2009, Trystan's parents went to see Ms. Marin-Tucker for a follow-up. In a review of Trystan's systems, Ms. Marin-Tucker noted no seizures, weakness, or tics. Exhibit 1 at 57. She made no notation of tremors or twitching. Id. Upon neurologic examination, however, she found Trystan to be unable to grasp, sit, crawl, or make much eye contact and concluded that Trystan was "not normal for age." Id. Mr. Sanchez reported that there was "another child in the family with the same symptoms and doctors [could] find nothing wrong." Id. Ms. Marin-Tucker emphasized the importance of making the appointment with a neurologist as soon as possible. Id. at 58.

On November 12, 2009, Trystan was taken to see a neurologist, Dr. David J. Michelson. Id. at 140. Dr. Michelson recorded that Trystan was unable to sit independently, his hands stayed closed, and his feet went forward when at rest. Id. He noted that, at times, Trystan could hold his mouth open tightly and drool, but at other times he could chew and swallow well. Id. While Trystan had previously held his right arm stiffly behind him episodically, he had not done this lately. Id. Dr. Michelson's review of systems was positive for muscle spasms, global developmental delay, weakness, walking problems, and constipation. Id. Dr. Michelson noted that Trystan suffered from "global developmental delay of unclear etiology, though a genetic predisposition is suspected based on the family history and a [central nervous system] cause is suggested by the physical exam findings." Id. at 140-41.

An MRI performed on December 8, 2009, found abnormalities in Trystan's basal ganglia. Id. at 130. At this time, physicians were still considering biotin-dependent basal ganglia disease as the most likely diagnosis, though a metabolic disorder, such as Leigh's syndrome, started to be considered. Id. at 130-33.

Over the course of the next five years, doctors could not identify the specific cause of Trystan's symptoms. In 2011, Dr. Jennifer Friedman evaluated Trystan and considered multiple diagnoses. A mitochondrial disorder was considered unlikely because Trystan's muscle biopsy indicated nothing more than mild impairments in mitochondrial function. See exhibit 10 at 7.

Trystan was evaluated by a specialist in mitochondrial disorders, Dr. Richard Haas, for the first time in August 2012. Exhibit 26 at 1-4. Dr. Haas

ordered sequencing of Trystan's mitochondrial DNA to assist in the diagnosis.[4] Id. at 3. Trystan was seen again in March 2013 and the results from the mitochondrial sequencing were discussed. The results indicated some heteroplasmy[5] in a previously unreported variant. Id. at 6. However, this was "unlikely to be the cause of Trystan's disease." Exhibit 52 at 2. In a subsequent appointment, Dr. Haas recommended that Trystan have whole exome[6] sequencing performed on his nuclear DNA. Id.

The cause of Trystan's symptoms was finally identified in late 2014 (three years after the petition was filed), when the results from Trystan's whole exome sequencing revealed two different heterozygous mutations in Trystan's DNA. Exhibit 59 at 1. These mutations were predicted to cause the same mitochondrial disorder that was under consideration in Trystan's case. Id. Based on these results, Dr. Haas confirmed Trystan's diagnosis of Leigh's syndrome. Exhibit 62 at 5.

Trystan continues to suffer from developmental delays and other symptoms such as dystonia and seizures. Exhibit 136 at 8; exhibit 140. Trystan can only babble, though he can say the word "mom," and he relies on signs to communicate his wants. Exhibit 136 at 8. Fortunately, his physicians consider his progression to

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[4] As reviewed in section IV.A., below, mitochondria are subcellular organelles. Interestingly, mitochondria have their own DNA, though it is a small portion of the cell's total DNA (the rest being contained in the nucleus of the cell). Benjamin A. Pierce, Genetics: A Conceptual Approach 122 (5th ed. 2014). Because Trystan was suspected to have a genetic disease of his mitochondria, and because the mitochondrial genome is much smaller in size than the nuclear genome, the physicians, presumably, decided to start looking there.

[5] Because of how mitochondrial DNA is replicated, not all mitochondrial DNA in a given organism is identical. Instead, some mitochondria in an organism may have a mutation in the mitochondrial DNA while others will not. This is referred to as *heteroplasmy*. Robert C King, Pamela K Mulligan, & William D. Stansfield, A Dictionary of Genetics 216 (8th ed. 2013). The proportion of cells with the mutation is related to the likelihood that the mutation is associated with disease. Id.

[6] Exome sequencing is genetic sequencing limited to the exons in the genome. Exons are the expressed portion of the gene, the part that becomes proteins. A Dictionary of Genetics at 160.

be "not as severe" as the typical progression for Leigh's syndrome. Exhibit 140 at 6.

II. Procedural History

Trystan's parents filed a petition for compensation under the Vaccine Act on October 17, 2011. The respondent, the Secretary of Health and Human Services, filed his Rule 4(c) report on February 28, 2012, challenging the Sanchezes' entitlement to compensation. Because there existed a factual dispute regarding when Trystan's symptoms began, a one-day fact hearing was held on May 15, 2012, in San Diego, California. Following the hearing, the parties were ordered to begin the process of agreeing upon uncontroverted facts regarding the onset of Trystan's condition. Order, issued May 29, 2012. The parties were able to submit a joint statement of uncontroverted facts on February 7, 2013. Based in part on this joint statement, the undersigned entered the ruling finding facts on April 10, 2013.

The parties proceeded to procure expert reports that incorporated the factual findings.[7] A three-day hearing to hear testimony from the expert witnesses was set for September 10-12, 2014. Order, issued Jan. 31, 2014. Three months before the scheduled hearing, the Sanchezes requested a continuance for the hearing so that Trystan could have the whole exome sequencing performed on the recommendation of Dr. Haas. Pet'rs' Rep., filed June 23, 2014. The Sanchezes hoped that the sequencing would provide clarity as to Trystan's illness. Id. Based on the Sanchezes' request, the hearing dates were postponed to May 2015. Order, issued July 8, 2014. The Sanchezes were ordered to file the results of the genetic testing as soon as they became available. Order, issued July 21, 2014.

The Sanchezes filed testing identifying Trystan's genetic mutations on January 23, 2015. During the ensuing status conference, the parties noted that they needed additional expert reports, although they also decided to retain the May 2015 hearing date at that time. Order, issued Feb. 4, 2015. On February 20, 2015, the

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[7] Although this decision does not mention each report from every expert, the undersigned has reviewed and considered all reports submitted into evidence. See Moriarty v. Sec'y of Health & Human Servs., 844 F.3d 1322, 1330 (Fed. Cir. 2016) (noting that the Vaccine Act requires a special master to consider all relevant medical and scientific evidence of record).

Sanchezes filed a status report requesting that the May 2015 hearing be postponed. The Secretary did not object to this request. Order, issued Mar. 3, 2015. Accordingly, the undersigned cancelled the May 2015 hearing and scheduled a status conference for late April 2015 to discuss the next steps. Id.

During the April 2015 status conference, the undersigned stated a concern that the newly-filed information regarding Trystan's genetic mutations undermined the Sanchezes' claim of a vaccine-injury because Trystan's clinical course may be consistent with what is expected based on the mutations alone. Order, issued May 8, 2015, at 1. The undersigned encouraged the Sanchezes to develop evidence that would show that Trystan was worse than would be otherwise expected for someone with his genetic mutations. Id. Accordingly, the Sanchezes requested additional time to procure genetic testing from Trystan's siblings since the results might shed light on how Trystan's disease course may be different than what can be expected for someone with his same genetic mutations. Id. The Sanchezes' request was granted and a status conference was set for June 2015, to discuss the results from the new genetic testing and the Sanchezes' next steps. Id. at 1-2.

On June 23, 2015, the Sanchezes filed a status report stating that the additional genetic testing would not be complete before the end of July 2015, and that the Sanchezes currently had an appointment scheduled with their treating physician for late August 2015, to discuss the results of this additional genetic testing. The undersigned set a status conference for the end of September 2015. Order, issued June 24, 2015.

During the September 2015 status conference, the parties discussed the need for additional expert reports in light of the new information regarding Trystan's genetic mutations. Order, issued Oct. 1, 2015. Over the course of the next year, both the Sanchezes and the Secretary filed additional reports from their respective experts as well as their prehearing briefs. See generally ECF Nos. 127-195.

In the pre-hearing status conference, the undersigned expressed a concern that without management, the four-day hearing — a duration to which both parties had was agreed — might not provide sufficient time to take testimony from the six expert witnesses. In such instances, it is often necessary to schedule a continuation of the hearing. Continuations are incredibly tolling on the Vaccine Program. They delay the adjudication of petitioners' claims for, often, at least a year as the parties attempt to schedule the participation of their witnesses (often, medical professionals with active practices and obligations in other cases), themselves, and the special master. They also delay the adjudication of other cases. In addition, they impose costs in the form of attorney fees, expert fees, and travel costs.

To ensure that all testimony was taken during the four-day hearing, after consulting with the parties, the undersigned defined the amount of time the parties had to elicit testimony from their own witnesses on direct examination, or from the other party's witness on cross-examination. See order, issued Nov. 27, 2017, at 3. Because the undersigned often asks questions of the parties' expert witnesses, the undersigned limited the time for his own questions. In total, for the four-day hearing, the Sanchezes were allotted 12.5 hours; the Secretary 8.75 hours; and the undersigned 4 hours. Id.[8] The undersigned considers the time allotted to have been sufficient to provide each party a full and fair opportunity to present its case. See Vaccine Rule 3(b)(2). Furthermore, the undersigned found the time limits to be reasonable for the evidence that needed to be taken in this specific case. See Vaccine Rule 8(a) ("The special master will determine the format for taking evidence and hearing argument based on the specific circumstances of each case"). Cf. D'Tiole v. Sec'y of Health & Human Servs., 726 F. App'x 809, 812 (Fed. Cir. 2018) (citing 42 U.S.C. § 300aa-12(d)(3)(B)(v)) (noting that the decision to hold an evidentiary hearing is statutorily committed to the discretion of the special master).

A four-day hearing was held on December 4-7, 2017. During the hearing, the Sanchezes solicited testimony from their two expert witnesses: Dr. Lawrence Steinman and Dr. Dmitriy Niyazov. The Secretary solicited testimony from four expert witnesses: Dr. Gerald Raymond, Dr. Stephen McGeady, Dr. Edward Cetaruk, and Professor Dean Jones. The hearing ended half a day early, with both parties and the undersigned not using all of their allotted time

III. Standards for Adjudication

Trystan's condition does not constitute a Table injury under the Vaccine Act. As an "off-Table Injury," the Sanchezes must demonstrate that the vaccine caused or significantly aggravated Trystan's injury. 42 U.S.C. § 300aa-11(c)(1)(C)(ii).

The Sanchezes' burden of proof as an off-Table injury is explicitly defined by Congress. The Act provides that a petitioner must show, by a preponderance of the evidence, that the vaccine sustained or significantly aggravated the illness or injury. See 42 U.S.C. § 300aa–13(a)(1) and 42 U.S.C. § 300aa-11(c); see also Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010)

[8] The fraction of the total time was petitioners: one-half, respondent: one-third, and special master: one-sixth.

(noting that petitioners must prove causation by the traditional tort standard of preponderance). As for what is necessary to meet this burden, the statute itself only requires that the conclusion of the court or special master may not be "based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion." 42 U.S.C. § 300aa-13.

Instead, special masters must consider all the evidence and decide whether the causal link between the vaccine and the injury was logical and legally probable. See Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994) ("The sole issues for the special master are, based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the [] injury"); Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("Causation in fact requires proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury"); Hines v. Sec'y of Health & Human Servs., 940 F.2d 1518, 1525 (Fed. Cir. 1991) ("causation in fact requires proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury").

In establishing whether preponderant evidence of causation exists, fact-finders often divide the analysis into two parts. First, is it biologically plausible for the vaccine to cause the alleged injury? If this plausibility, or "general causation" inquiry, is satisfied, then the petitioners must next prove that the vaccine actually caused the alleged symptoms in her particular case. See Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1356 (Fed. Cir. 2006) (finding this two-part test to state a petitioner's burden of proof in claims of off-Table vaccine injury correctly); see also Moreno v. Sec'y of Health & Human Servs., No. 95-706V, 2005 WL 6120645, at *1 (Fed. Cl. Apr. 27, 2005) (applying this same two-stage analysis).

Regardless of the framework applied by the special master, the outcome of any decision rests simply on the question of whether there exists preponderant evidence of causation in the case at hand; special masters must not create bars to compensation that do not exist in the statute itself. See, e.g., Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006) (rejecting a test that required "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities"). In other words, the evidence must be considered in whole and conclusions regarding causation should involve an analysis of the entire picture. See, e.g., Knudsen, 35 F.3d at 549; see also Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1357 (Fed. Cir. 2010) (endorsing the special master's

consideration of a factor unrelated to a vaccine in determining whether a petitioner had presented sufficient evidence of causation-in-fact).

IV. Overview

A. Introduction to Genetic Issues

The parties agree that Trystan was born with two mutations in his nuclear[9] DNA. The parties also agree that but for these mutations, Trystan would not have developed Leigh's syndrome. Where they disagree is whether the vaccinations Trystan received on February 5, 2009, constituted a substantial factor in his development of Leigh's syndrome.

The specifics of Trystan's genetic condition are discussed more thoroughly in section V.C., below. However, a brief introduction is appropriate here for the purpose of understanding how the mutation, the vaccination, and the disease are all potentially interrelated.

Trystan inherited two different mutations in his nuclear DNA, one from his mother and one from his father. Exhibit 59 at 1. While the mutations are different, they both affect the same gene encoding subunit A of the succinate dehydrogenase enzyme (SDH). The combination of the two distinct mutations to the same SDHA gene is referred to as a *compound heterozygous* SDHA mutation.[10] See A Dictionary of Genetics at 98.

SDH is one enzyme (an enzyme is a type of protein) in a larger chain of mitochondrial enzymes that are responsible for creating cellular energy, a key function of the mitochondria more generally. See Dorland's Illustrated Medical Dictionary 1795 (32d ed. 2012). Consistent with the critical role of energy production to the sustenance of life, and the role of the SDH enzyme in energy production, the SDH enzyme is essential for life. An examination of the SDHA

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[9] Although the SDH enzyme is located in the mitochondria, it is encoded by nuclear DNA, not mitochondrial DNA. See exhibit 148 (Shamima Rahman and David Thorburn, Nuclear Gene-Encoded Leigh Syndrome Overview, GeneReviews (July 5, 2017), https://www.ncbi.nlm.nih.gov/books/NBK320989) at 1-2.

[10] Had Trystan inherited the same mutation from both his mother and his father, he would have a *homozygous* mutation. See A Dictionary of Genetics at 224.

gene in other species indicates that the coding of the gene has highly conserved regions. See, e.g., exhibit H, tab 28 (R. Horvath et al., Leigh Syndrome Caused by Mutations in the Flavoprotein (Fp) Subunit of Succinate Dehydrogenase (SDHA), 77 J. Neurology Neurosurgery Psychiatry 74-76 (2006)) at 2.[11] Conservation of genetic code is indicative of the code's importance; it hints that changes to the code are not conducive to life. See A Dictionary of Genetics at 100.

Although Trystan has two mutations and has been diagnosed with Leigh's syndrome, not all SDHA mutations result in Leigh's syndrome, and not all cases of Leigh's syndrome are the result of SDHA mutations. See exhibit H, tab 7 (Thomas Bourgeron et al., Mutation of a Nuclear Succinate Dehydrogenase Gene Results in Mitochondrial Respiratory Chain Deficiency, 11 Nature 144 (1995)) at 4 (noting that SDHA mutations can lead to cardiomyopathy and Kearns-Sayre Syndrome); exhibit 148 (Rahman) at 4 (noting that SDHA mutations are a small fraction of the types of mutations associated with Leigh's syndrome). Cf. Oliver v. Sec'y of Health & Human Servs., No. 2017-2540, 2018 WL 3945586, at *8 (Fed. Cir. Aug. 17, 2018) (Newman, J., dissenting) (noting that the lack of a one-to-one correspondence between an SCN1A mutation and Dravet syndrome allowed for the conclusion that a vaccine reaction was a substantial factor in the onset of the disease).

Importantly, Leigh's syndrome is not so much a specific pathology with an expected course as it is a label applied to a variety of pathologies that manifest somewhat similarly and, historically, is hallmarked by the observation of characteristic brain lesions on post-mortem examination. Tr. 792. Using this definition for Leigh's is partly historical since at the time the disease was first characterized, genetic testing and MRI were not available. As Dr. Haas notes, with regard to Trystan, "Leigh Syndrome usually refers to a severe neurological disorder that often presents in the first year of life and is characterized by progressive loss of mental and movement abilities and typically results in death within a couple years." Exhibit 140 at 5. However, Dr. Haas also notes that "it may be used as an umbrella term for many mitochondrial disorders" and, as a consequence, "the variable presentation makes a prognosis challenging." Id.

[11] Citations to research articles reference the page number of the PDF exhibit, not the page number of the published article.

B. The Sanchezes' Argument

The Sanchezes acknowledge that absent Trystan's mutations he would not have Leigh's syndrome today; the vaccines were insufficient to cause Trystan to develop Leigh's syndrome. See Pet'rs' Preh'g Br. at 23 (noting that Trystan's SDHA mutations provided the susceptibility for the Leigh's syndrome). However, the Sanchezes also argue that the vaccinations he received on February 5, 2009, either caused his genetic condition to be expressed or, alternatively, significantly aggravated the course of his disease. Pet'rs' Preh'g Br. at 29. In other words, the Sanchezes argue that the vaccination was a substantial factor in Trystan's disease course.[12]

C. The Secretary's Argument

The Secretary contends the evidence in the record is not consistent with a conclusion that the vaccination caused or significantly aggravated Trystan's condition. More specifically, the Secretary considers the Sanchezes' theories for how the vaccination could have caused or significantly aggravated Trystan's condition to not be sufficiently plausible under the standards set forth by the Vaccine Act and the Federal Circuit. Resp't's Preh'g Br. at 8-11. Furthermore, the Secretary argues that the timeline between the vaccination and the onset of Trystan's disease is not consistent with a conclusion that the two represent a

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[12] The Sanchezes argue that this case does not involve a significant aggravation analysis. Pet'rs' Preh'g Br. at 16-17. Although the Sanchezes offer a significant aggravation analysis in the alternative, they argue that the question at hand is simply whether Trystan's vaccinations were a substantial factor in Trystan's disease course. Id. The Federal Circuit has held that the six-step test put forth in Loving is the appropriate analysis for examining claims of significant aggravation. W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (referencing Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009)). Nonetheless, as Judge Bruggink of the Court of Federal Claims has pointed out, the Loving framework does not provide a straightforward method of analysis for cases in which a vaccinee had a preexisting genetic mutation. See Barclay v. Sec'y of Health & Human Servs., 122 Fed. Cl. 189, 193 (2015).

Because the Loving test for significant aggravation incorporates the requirement of establishing but-for causation, regardless of which construct is followed, the outcome here is the same. As explained in the text, the Sanchezes have not established that Trystan declined in an appropriate temporal window.

logical sequence of cause and effect. Id. at 11-12. The Secretary further argues that the Sanchezes cannot show that Trystan's current condition is worse than it would have been but for the vaccination. Id. at 13-14.

V. Analysis

The analysis consists of three sections. First, the undersigned evaluates whether vaccinations can cause the manifestation of Leigh's syndrome. This is the equivalent of the first Althen prong. Second, the undersigned determines whether the vaccination did harm Trystan in the manner proposed. This analysis essentially combines the second and third Althen prongs. Third, the undersigned considers Trystan's genetic mutations and how the genetic mutations have affected Trystan's development.

A. The Sanchezes' Medical Theory of Causation

The Sanchezes argue that Trystan's Leigh's syndrome was brought on by the vaccinations he received on February 5, 2009. To demonstrate that vaccinations can cause the onset of Leigh's syndrome, the Sanchezes provide evidence showing that the onset of Leigh's syndrome is associated with a *decompensating event*[13] and that vaccination could cause such a decompensating event. Though a link between vaccination and the onset of Leigh's syndrome has not been established to the standard of medical certainty, for the reasons elucidated below, the evidence presented is sufficient to conclude that the Sanchezes' theory is plausible insofar as it is consistent with contemporary understanding of the biological systems at play. Accordingly, the Sanchezes have met their statutory burden on this element as the Federal Circuit has defined it. See Hibbard v. Sec'y of Health and Human Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012) (noting that petitioners' burden is to provide a "viable medical theory by which a vaccine can cause the injury claimed by the petitioner").

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[13] Decompensation is a period of regression that is frequently seen in cases of Leigh's disease. Exhibit 148 (Rahman) at 1. Dr. Raymond testified that decompensation in individuals with Leigh's syndrome is clinically obvious and is characterized by encephalopathy, decreased consciousness, weakness, and motor difficulties. Tr. 794-95. Dr. Niyazov largely agreed with this characterization of decompensation, but noted that the decompensation can be followed by periods of prolonged stabilization and possibly even improvement. See Tr. 417.

The first manifestation of Leigh's syndrome is known to follow an intercurrent illness in many, if not most, cases. Exhibit 148 (Rahman). The parties and their respective experts do not appear to dispute this fact and the medical literature in the record indicates that this is part of the canonical presentation of Leigh's syndrome. See, e.g., exhibit 148 (Rahman) at 2 ("Onset is typically between ages three and 12 months, frequently following a viral infection"). As for why a viral illness can precipitate onset of Leigh's syndrome, Jeffrey D. Kingsley et al., in the journal Pediatrics, note that:

> The metabolic homeostasis of individuals with inborn errors of metabolism is tenuously balanced and may be easily compromised by any degree of superimposed metabolic stress. Inadequate food intake, depleted energy stores, and impaired or excess formation of metabolic components place considerable stress on these individuals' ability to achieve a metabolic balance. Febrile episodes caused by infections or other inflammatory processes further accentuate this stress and may result in a significantly amplified degree of morbidity and mortality in affected individuals.

Exhibit 99 (Jeffrey D. Kingsley, Immunizations for Patients with Metabolic Disorders, 118 Pediatrics e460 (2015)) at 5.[14]

Thus, the pertinent question appears to be whether vaccination can induce the type of metabolic stress that could cause decompensation.

A substantial portion of the pre-hearing briefs as well as the hearing was spent arguing how exactly Trystan's vaccinations, on a mechanistic level, may have caused decompensation. The Sanchezes proffered three different mechanisms that may have mediated the link between Trystan's vaccines and the decompensation: 1) ADP-ribosylation, 2) alum, and 3) oxidative stress. The Secretary (though not always his expert witnesses) argued against these theories. Testimony concerning these theories consumed a substantial portion of the hearing in this case.

For all this debate regarding the mechanisms that might be involved, the conclusion that the Sanchezes have met their burden to present a plausible medical theory explaining how Trystan's vaccines may have caused his injury requires only two premises to be more-likely-than-not. First, that the vaccine that Trystan received is known to sometimes cause fever (regardless of the mechanistic causes

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[14] Kingsley et al. were commenting on metabolic disorders more generally, not Leigh's syndrome specifically.

of that fever). Second, fever can cause decompensation in someone with a pre-existing mitochondrial disease.

A review of the evidence makes apparent that while the Secretary stridently opposed the proposed mechanisms, the Secretary did not rebut either of these general premises. Furthermore, the evidence indicates that both premises are likely to be consistent with contemporary medical thought.

As for the first premise, there appears little question that the vaccines Trystan received sometimes cause fever. Trystan's undisputed fever and crying following the vaccine appears on the package insert for that same vaccination, exhibit 92, and even Dr. McGeady characterized Trystan's immediate reaction to the vaccine to be "often seen." Tr. 729. Beyond plausibility, there appears to be no meaningful debate about the fact that the vaccines that Trystan received actually *did* cause him to develop a fever. See Tr. 734 (Dr. McGeady testifying that "I do think [the vaccination] had something to do with the fever)."[15]

As for the second premise, there also appears agreement, or at least not meaningful debate, that fever—including fever following vaccination—can result in decompensation.

For instance, Kingsley et al. warn physicians that they should closely monitor the possibility of fever in vaccine recipients who have metabolic disease. Id. at 8 ("Given the pathophysiologic implications of immunization, it can be seen that the febrile response, the anorexia, or both may contribute to a metabolic decompensation in these patients with potentially serious consequences"). The Kingsley authors appear not to be alone in their concern for how febrile responses

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[15] The uncontroverted premise that the vaccines administered on February 5, 2009, caused Trystan to suffer a fever distinguishes this case from one in which another special master found that a petitioner had not presented a viable medical theory connecting a FluMist vaccine to metabolic decompensation in a child with Leigh's syndrome and a mutation in her mitochondrial DNA. See H.L. v. Sec'y of Health & Human Servs., No. 10-0197V, 2016 WL 3751848, at *22 (Fed. Cl. Spec. Mstr. Mar. 17, 2016), mot. for rev. denied, 129 Fed. Cl. 165 (2016), aff'd, 715 F. App'x 990 (Fed. Cir. 2017). In H.L., the special master found that *absent a fever*, there was no evidence that a vaccine "can contribute to a regression or decompensation in a patient with a mitochondrial disease." Id. at 16. Thus, the finding that H.L. did not suffer a fever in response to the FluMist vaccination precluded the viability of her theory in that case. That is not the case here.

to vaccination could have deleterious effects for children with inborn metabolic disorders. They note that the Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommend that individuals with "evolving neurologic conditions" not be vaccinated with DTaP until a treatment regimen has been established and the condition stabilized. Id. at 4. These committees further recommend that antipyretic medication be administered concurrently with vaccination to reduce the possibility of post-vaccination fever. Id. These precautions were not taken with Trystan because his inborn metabolic disease was not known at that time.

The Secretary did not present an expert in mitochondrial diseases and nothing in the record from the Secretary indicates that he took the position that fever is not linked to metabolic decompensation in children with inborn mitochondrial disorders. Even more, a review of other cases in the Vaccine Program indicates that the Secretary has, in previous cases, not contested that fever can cause metabolic decompensation in children with mitochondrial disorders. See H.L., 2016 WL 3751848, at *7 (noting that both parties' experts agreed "that metabolic decompensation can be caused by a fever").

Instead, in the present case, the Secretary's challenge targeted the specific mechanisms, whether they be mediated by ADP-ribosylation, alum, oxidative stress, or in the opinion of one of the Secretary's experts, Dr. McGeady, complement fixation.[16] See Tr. 729 (Dr. McGeady hypothesizing that complement fixation explains why Trystan displayed fever and inconsolable crying after the February 5, 2009 vaccinations). While it is true that none of the Sanchezes' theories are perfect, the law does not require them to be. See Knudsen, 35 F.3d at 549 ("[T]o require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program"). It is not the Sanchezes' burden to show *how* the vaccines caused the onset of Trystan's illness, but it is their burden to show that they *can* cause Trystan's illness. See Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1384 (Fed. Cir. 2012). The Sanchezes have met this burden.

[16] The Secretary understandably dedicated a substantial amount of his case arguing against the specific mechanisms proposed by the Sanchezes because they dedicated a substantial portion of their case arguing those specific mechanisms. Compare Pet'rs' Preh'g Br. at 17-37 (setting forth the Sanchezes' medical theories) with Resp't's Preh'g Br. at 8-11 (rebutting the Sanchezes' medical theories).

B. Evidence that the Vaccine Caused Trystan's Injury

While the Sanchezes have presented sufficient evidence to establish that Trystan's vaccines *could* cause the initial manifestation of his Leigh's syndrome, they have not established that it actually *did*. This is simply due to the fact that the timing of the manifestation of Trystan's Leigh's syndrome was not consistent with the vaccination being a factor in his development of the disease.

On its face, the Sanchezes' argument that the timing is indicative of vaccine causation is somewhat deceptive. The Sanchezes and their experts often incorporate into their argument the premise that February 5, 2009, marked a turning point in Trystan's development, wherein nothing was ever the same again.

By doing so, the Sanchezes and their experts attempt to mirror the facts of the case study presented in Poling et al. See exhibit 84 (Jon S. Poling et al., Developmental Regression and Mitochondrial Dysfunction in a Child with Autism, 21 J. Child Neurology 170-72 (2006)). This article recounts the experience of a young girl with asymptomatic mitochondrial dysfunction, who developed a fever after immunizations to DTaP, Hib, MMR, polio, and varicella. Id. at 2. Within 48 hours after immunization, the young girl developed a fever of 102°F and was crying inconsolably. Id. Four days later, the child could no longer climb stairs and was having episodes of opisthotonus. Then, over the course of several months, the child became increasingly less responsive verbally. Id. The Sanchezes argue that, like the young girl in Poling, the vaccinations marked a turning point in Trystan's life wherein nothing was ever the same again.

This premise concerning the timing appears consistently throughout the record. Trystan's response to the vaccine has been referred to as the beginning of "a downward cascade." Tr. 278. Other times, the Sanchezes' experts stated that Trystan was healthy before the vaccine and that the deterioration began immediately after. See Tr. 292 ("he seemed to be a healthy well child and following that February 5th immunization . . . he had neurologic deterioration"); Tr. 338 (noting that before the immunization Trystan seemed like a healthy child and after the vaccination he "started having deterioration"). On other occasions, the claim was that it began gradually after the vaccination. E.g., exhibit 68 at 8 ("developmental regression was slowly developing ever since the crying and fever took place as the result of the vaccination"). Regardless of the specific language, the Sanchezes' experts have assumed the premise that Trystan "was never the same after that first [February 5, 2009] shot." Tr. 951.

Though the Sanchezes and their experts may believe that there is "no doubt [that Trystan's neurological deterioration] began on February 5th," Tr. 293, the

evidentiary record does not support this premise that is so central to the Sanchezes' argument.[17] Instead, as reviewed in section I.B.3, above, the record indicates that Trystan's loss of skills did not occur before May 2009, at the earliest. The sequence of events in Trystan's life make his case very different from the girl in the Poling article. Cf. Kreizenbeck v. Sec'y of Health & Human Servs., No. 08-209V, 2018 WL 3679843, at *28 (Fed. Cl. Spec. Mstr. June 22, 2018) (explaining that the facts in that case were "completely distinguishable" from the young child presented in the Poling article), mot. for rev. filed, July 20, 2018.

Accordingly, approximately three months passed between when Trystan received the February 5, 2009 vaccinations and the earliest possible onset of his neurological regression. The question at bar is whether a delay of this magnitude is consistent with vaccine-causation. A review of the literature indicates that it is not.

As an initial matter, the undersigned recognizes that the available evidence for the appropriate time between a decompensating event and the onset of neurological symptoms is imperfect. Nonetheless, the available evidence is sufficient to conclude that, more likely than not, Trystan's Leigh's syndrome, which presented no earlier than the beginning of May 2009, was not the result of the vaccinations he received on February 5, 2009, approximately three months earlier.

The most precise evidence of the appropriate timing between a decompensating event and the onset of neurological symptoms is presented in Edmonds et al. Exhibit 75 (Joseph L. Edmonds et al., The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration With Infection, 128 Archives Otolaryngological Head Neck Surgery 355-62 (2009)). In

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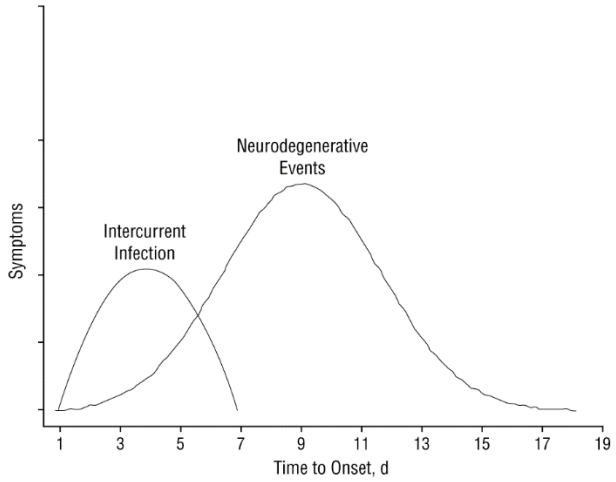
[17] Dr. Niyazov's and Dr. Steinman's assumption of a relatively early onset based upon parental affidavits and testimony make the present case comparable to multiple autism cases in which a special master refrained from crediting an expert report that assumed facts not consistent with medical records. E.g., Rogero v. Sec'y of Health & Human Servs., No. 11-770V, 2017 WL 4277580, at *42 (Fed. Cl. Spec. Mstr. Sept. 1, 2017) (noting that the petitioners' failed to prove their claim of causation because their experts relied on incorrect assumptions), mot. for rev. denied, slip op. (Jan. 11, 2018), aff'd, No. 2018-1684, 2018 WL 4355990 (Fed. Cir. Sept. 12, 2018).

the Edmonds article, the authors found that in most cases the neurological setback (in the Edmonds study, hearing loss) occurred between three to seven days following the intercurrent infection, though in a few patients the neurological setback occurred early in the course of the infection. Id. at 6. Based on the article, it appears that in no case did the neurological setback occur more than seven days following the infection. Id.

There has been some confusion in this case, and in others, regarding the significance of Figure 3 of the Edmonds paper and thus, for clarity, the figure is reproduced below.



Id. at 7.

The figure's caption describes it as showing "timing of infection-associated neurologic setbacks in patients with mitochondrial disease." Id. The distribution demonstrates that there is a stochastic nature to the time when neurodegenerative events begin in relation to the intercurrent infection that is canonically associated with the decompensation. Consistent with the data reviewed above, the neurodegeneration sometimes occurred early in the course of the infection, but most frequently followed the infection by three to seven days.

The confusion appears to be the result of the relationship of the figure and the distribution of the actual results found in the paper. The Sanchezes, in their pre-trial brief, argue that Edmonds demonstrates "neurodegeneration occurring following infection in patients with mitochondrial disorders over a period extending to 19 days." Pet'rs' Preh'g Br. at 51. The Federal Circuit, in Paluck v. Sec'y of Health & Human Servs., interpreted the figure to show that "in at least one patient in the Edmonds study, the neurological setback did not occur until nineteen days after infection." 786 F.3d 1373, 1383 (Fed. Cir. 2015).

However, as Dr. Raymond cogently explained, the figure is merely a schematic, not a representation of the raw data and this distinction is important when considering the significance of the figure. Tr. 835-36. The authors expressly state: "In a few patients (3/13), the neurologic setback occurred early in the course of infection. In most patients (10/13), the neurologic event occurred 3 to 7 days after the onset of infection." Exhibit 75 (Edmonds) at 6. Thus, it follows that *no* patient showed the onset of neurodegeneration more than 7 days following the onset of the infection. See Tr. 835 (Dr. Raymond making the same point); Tr. 512-13 (Dr. Niyazov confirming, on cross-examination, that no patient in the study had the neurological setback more than seven days after the onset of the infection). Had the authors observed that one of 13 patients presented with neurodegeneration 19 days after the onset of the infection, general principles of sampling and inferential statistics suggests that some patients in the broader population have onsets even longer than 19 days since a latency of that duration appeared in the small sample of 13 patients. However, that is not what the article says. Instead, the authors find that no patients had onsets greater than 7 days following infection and Figure 3 appears to show that the authors understand that there are likely patients in the general population with onsets beyond 7 days, though how much longer than 7 days is merely just an educated guess. Nonetheless, a 19-day latency appears to be, literally, off-the-charts, at least in the opinion of the authors.

The authors from exhibit 86 (John Shoffner et al., Fever Plus Mitochondrial Disease Could be Risk Factors for Autistic Regression, 25 J. Child Neurology 429-34 (2010)) appear to generally agree with this estimation of the appropriate timing between the intercurrent infection and the onset of neurodegeneration. Importantly, the Shoffner paper does *not* present direct evidence of the appropriate timing between the infection and the onset of neurodegeneration. Instead, for the purposes of their study, the authors assume autistic regression within two weeks of a fever as being caused by the fever. Exhibit 86 (Shoffner) at 2. The authors do not state their basis for this two week timeframe nor how liberal or conservative the timeframe is in associating autistic regression to an infection based on timing alone. Thus it is difficult to weigh the significance of the authors' opinions that an interval of less than two weeks is consistent with causation while an interval of greater than two weeks is not. Nonetheless, it is consistent with the broader conclusion that the appropriate interval is approximately two weeks or less.

The Poling et al. case study, referenced earlier, also provides some useful information about what may be expected in regards to timing. See exhibit 84 (Poling) at 1. In that case, the young girl began demonstrating clear loss-of-skills within a week of the vaccination. Poling, as a case study appearing in a medical

journal, is limited in its contribution.[18] Nonetheless, it provides further support for the rough timeline presented in Edmonds and Shoffner.

Undoubtedly, Edmonds, Shoffner, and Poling are far from comprehensive studies of the appropriate onset timing. They do not lend themselves to a hard and fast deadline for when Trystan's symptoms would have had to develop following the vaccination, and the undersigned does not create one here. See Paluck, 786 F.3d at 1383 (holding that a hard and fast deadline of three weeks for a finding of causation under similar circumstances was arbitrary). Nonetheless, the undersigned must consider the evidence that as the post-vaccination interval extends beyond two weeks, the likelihood that the decompensation is attributable to a reaction to the vaccine, as opposed to another cause, drops. See Pafford, 451 F.3d at 1358 ("If, for example, symptoms normally first occur ten days after inoculation but petitioner's symptoms first occur several weeks after inoculation, then it is doubtful the vaccination is to blame").

To explain the delay between the vaccination and the loss of skills, the Sanchezes argue that detecting loss of skills in a six-month-old infant is difficult and thus—even if the temporal interval is almost always less than two weeks—there may be a substantial delay between when skills start being lost and when their loss is first noticed by a physician. Tr. 294-98. This point is worthy of serious consideration. The Edmonds, Shoffner, and Poling articles involved children appreciably older than Trystan developing forms of neurodegeneration that are more salient. This line of reasoning is buttressed by published research cited by the Sanchezes. This research indicates that, with regard to neurodegeneration in young children with a different—but more common—disorder, parents often become concerned months before the child is first diagnosed. See exhibit 71 (Anne-Marie Bisgaard et al., Is it Possible to Diagnose Rett Syndrome before Classical Symptoms Become Obvious? Review of 24 Danish Cases Born Between 2003 and 2012, 19 European J. Pediatric Neurology 679-87 (2015)). Furthermore, the research conveys anecdotes from parents noting that pediatricians and other treaters can often dismiss parents' concerns. Id. at 7-8. As Dr. Steinman notes, and the Secretary does not rebut, physicians will often consider a child missing one milestone as not a big problem and in such situations doctors will often try to calm parents' fears as oppose to stoke them. Tr. 294-98.

[18] As a legal case, Poling carries even less precedential value because it was an on-Table case.

The Sanchezes' argument that there may be a delay between when parents first notice something change in a child's development and when doctors diagnose a child is, on its face, reasonable. The cited literature only confirms that there is some truth to the claim. Furthermore, the undersigned believes that there is a non-insignificant chance that the Sanchezes relayed a concern at the May 13, 2009 visit with Dr. Brown that did not end up in the records. Nonetheless, this does not account for the three-month period where the records show no indication of Trystan having, or the parents being concerned about, a neurological condition. Instead, the concern appeared to be focused on Trystan's multiple colds. And, in fact, understanding what may have caused the manifestation of Trystan's disease requires a closer look at these very colds.

The Federal Circuit has endorsed special masters' consideration of alternate causes in determining whether petitioners have established their prima facie case. See Doe, 601 F.3d at 1357 (stating that the government can provide and the special master can consider evidence of "factors unrelated" in determining whether the petitioner established a prima facie case). Similarly, the absence of a "factor unrelated" may very well buttress a petitioner's claim of vaccine-causation (i.e., if nothing else can explain the onset of the disease other than the vaccine, the likelihood it was the vaccine is augmented).

Accordingly, as it pertains to this case, if Trystan did not experience any other decompensating events between the vaccination and the onset of his Leigh's syndrome, it may very well make his parents' claims of causation less improbable. However, the record shows that in the months leading up to when his loss of skills first manifested, Trystan suffered from multiple upper respiratory infections. See exhibit 1 at 48-53. These infections are known to precipitate mitochondrial decompensation. Exhibit 75 (Edmonds) at 3 (citing Robert K. Naviaux, The Mitochondrial DNA Depletion Syndromes, in Atlas of Metabolic Disease (W.L. Nyhan and P.T. Ozand eds., 1999)) ("a well-known clinical correlation of upper respiratory tract infections (URIs) . . . with neurodegenerative setbacks in mitochondrial disease exists");[19] see also Tr. 361 (Dr. Steinman noting that Trystan's infection could have contributed to the onset of his Leigh's syndrome). Trystan's URIs in March-May 2009 are entirely consistent with the infections

[19] Robert K. Naviaux is a colleague of Dr. Niyazov whom Dr. Niyazov characterized as "a very trusted and respected person, an expert in the field of mitochondrial disease." Tr. 377-78, 526.

being the intercurrent infection that induced his metabolic decompensation in May or June 2009. See also H.L., 715 F. App'x 990, 996 (ruling that the special master was not arbitrary in determining the sequence of events supported a finding that vaccinee's symptoms were more attributable to an URI than a vaccine-injury).

Here, the Sanchezes' inability, or failure, to address a conspicuous and probable alternate cause for the manifestation of Trystan's Leigh's syndrome weighs against a finding that the vaccination caused Trystan's injury. To be clear, the Sanchezes' failure to address the alternative cause does not per se preclude compensation, but it does weaken their claim of causation. See Pafford v. Sec'y of Health & Human Servs., 64 Fed. Cl. 19, 35 (2005) (noting that petitioners in causation-in-fact cases have "the obligation to successfully eliminate potential alternative causes of the alleged injury that have been identified in the record"), aff'd, 451 F.3d 1352 (2006); see also Munn v. Sec'y of Health & Human Servs., 970 F.2d 863, 865 (Fed. Cir. 1992) ("The claimant must prove by a preponderance of the evidence that the vaccine, and not some other agent, was the actual cause of the injury").[20] This omission on the part of the Sanchezes, in combination with the unlikelihood of a multiple-month delay between the vaccine and the onset of his neurodegeneration, makes a finding that the vaccine was, more likely than not, a substantial factor in Trystan's Leigh's syndrome untenable. Accordingly, the Sanchezes are not entitled to compensation under the Vaccine Act.

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[20] The Federal Circuit has left some ambiguity with regard to when a petitioner has an affirmative burden to rule out an alternative cause. Compare Pafford, 451 F.3d at 1366 (Dyk, J., dissenting) ("In summary, the majority incorrectly holds that petitioners, in order to make a prima facie case in off-Table cases, must establish a 'medically accepted temporal relationship' between vaccine and injury and eliminate other possible causes of the injury") with Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1152 (Fed. Cir. 2007) ("the petitioner does not bear the burden of eliminating alternative independent potential causes"). Notwithstanding this question over the allocation of the burden of proof, the undersigned's decision here finds that the Sanchezes have not established a prima face case of causation, independent of their failure to address the alternate cause.

C. Trystan's Condition but for the Vaccination

Because this decision finds that the Sanchezes have not established entitlement to compensation, the outcome of this decision does not depend on the Secretary's argument that Trystan was "nearly certainly destined to develop Leigh's syndrome due to this preexisting SDHA gene mutation." Resp't's Preh'g Br. at 14-15. Nonetheless, it is worth evaluating this issue for the purpose of preserving the record.

Because the genetic issues are complex, a general review of the material as well as a summary of the parties' positions may prove useful.

1. Genes, Proteins, and Disease

Proteins are the workhorse of our bodies. They are the structures that allow our neurons to fire and our muscles to contract. They convert food to energy and build the structures of our cells and our bodies. Everything our bodies *do* are done by proteins. See generally Dorland's at 1531 (explaining what proteins are and what functions they perform).

Proteins' broad range of capabilities is the result of their ability to take many forms. The form a protein takes is determined by the sequence of amino acids that comprise the protein. That sequence is determined by our genetic code: our DNA. In other words, proteins give life to the code. See id. at 490, 1644 (explaining how nucleic acid codes are transcribed and translated into proteins).

Our genetic code is the result of the comingling of our parents' code. A Dictionary of Genetics at 430. However, over time, variations in the code occur; that is partly how species evolve. See id. at 158, 308. Any time there is a permanent change in the sequence of the code, a *mutation* is said to have occurred. Exhibit J (Sue Richards et al., Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of The American College of Medical Genetics and Genomics and The Association for Molecular Pathology, 17 Genetics in Medicine 405-24 (2015)) at 2. Because of how our DNA is translated into proteins and the various roles of proteins in our bodies, these changes can have a broad range of effects. They may cause a fetus to be unviable at the earliest stages of life; they may cause a disease that does not manifest until 40 years of age; or they may cause no perceivable effect at all. They may also cause one's eyes to be a brilliant and unforgettable shade of green. Their effects are largely limitless. See generally Genetics: A Conceptual Approach at 493-533.

When a mutation can cause a disease, it is referred to as *pathogenic*. A Dictionary of Genetics at 345. The proclivity for a specific mutation to result in a

disease-state is the result of how the mutation affects the function of the protein for which it codes as well as the function of that protein in the body. Some mutations can cause drastic changes to the protein by creating, for example, a *frameshift* in the DNA code whereby the code is no longer legible. A Dictionary of Genetics at 175; exhibit J (Richards) at 9. Others might be the result of an early stop signal that results in a *truncated* protein; half a book, more or less. A Dictionary of Genetics at 319. However, mutations can also be relatively benign. For example, a mutation in DNA can, due to the way that DNA is translated into protein, result in no change in the actual protein. Alternatively, the mutation may result in a change in the structure of the protein that has no effect on its function. See Harris v. Sec'y of Health & Human Servs., No. 07-60V, 2011 WL 2446321, at *12 (Fed. Cl. Spec. Mstr. May 27, 2011) (discussing these types of benign mutations), mot. for review granted, decision rev'd, 102 Fed. Cl. 282 (2011), reinstated sub nom., Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994 (Fed. Cir. 2014).

Though there are benign mutations and deadly mutations, twin studies show that mutations frequently do not have a one-to-one correspondence with an outcome. See Snyder v. Sec'y of Health & Human Servs., No. 01-162V, 2009 WL 332044, at *46 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) (discussing the role of twin studies in showing the genetic cause of disease), mot. for review granted, decision rev'd, 102 Fed. Cl. 305 (2011), reinstated, 553 F. App'x 994 (Fed. Cir. 2014). In other words, *genotypes* (the genetic code) do not always necessitate *phenotypes* (the biological outcome). Id. The same mutation can readily result in one phenotype (be it a disease, a personality feature, or a physical feature such as height) in one individual, but be completely absent in another. The proportion of individuals that develop the phenotype associated with a mutation is referred to as *penetrance*. A Dictionary of Genetics at 347. For example, not every individual with a mutation in the BRCA1 gene develops breast or ovarian cancer because the mutation, though pathogenic, is *incompletely penetrant*. See id.; Tr. 1005.

Relatedly, some mutations can result in a wide spectrum of biological outcomes. In other words, the mutation *expresses* differently across individuals. For example, identical mutations associated with intellectual disability may result in individuals with a broad range of IQs. Like incomplete penetrance, *variable expressivity* is a hallmark of genetics. A Dictionary of Genetics at 161.

Incomplete penetrance and variable expressivity highlight the complexity of clinical genetics. Organisms are shaped not only by individual genes, but by their environment and the interaction of the environment with not only the mutated gene, but other genes that interact with the mutated gene. This makes it very

difficult to predict a clinical course based on a single mutation alone. See exhibit J (Richards) at 16.

2. Trystan's SDHA Mutations

As reviewed above, Trystan inherited two heterozygous mutations in his SDHA gene. Because of the nature of the mutations and their effect on the SDHA protein, the mutations are considered pathogenic. The parties dispute whether these two mutations made Trystan's disease a *fait accompli*.

To understand the potential effect of Trystan's inherited mutations on Trystan's clinical course, it is important to review Trystan's specific mutations and what is known about them.

Trystan's two mutations in his DNA are referred to as c.1571C>T and c.667delG. Exhibit 59 at 1. The first indicates that at location 1571 in the gene, a cytosine (C) has been replaced by a thymine (T). The second indicates that a guanine (G) that is supposed to be present at position 667 has been deleted. In the case of the first, this mutation changes the nucleic acid code so that where there is supposed to be an alanine in the protein, the cell now puts a valine (p.Ala524Val). In the case of the second, the mutation changes the nucleic acid sequence in a manner that creates a premature stop signal in the place of a signal for an amino acid. In other words, the cell believes that no more of the nucleic acid chain needs to be translated into amino acid, resulting in a shortened, or truncated, protein (p. Asp223IlefsX3). For consistency, all references are made to the locations of mutations in the DNA (in Trystan's case, c.1571C>T and c.667delG).

The result of these mutations was that Trystan's SDH enzyme cannot function quite right. However, the relationship between the mutation and Trystan's clinical condition is not easily predicted. Both parties submitted literature to assist in the determination of how Trystan's mutations may speak to his expected prognosis. A review of some of these articles and their findings is appropriate:

Exhibit H, tab 7 (Thomas Bourgeron et al., Mutation of a Nuclear Succinate Dehydrogenase Gene Results in a Mitochondrial Respiratory Chain Deficiency, 11 Nature 144-49 (1995)) presents the first account of a mutation in SDHA being associated with a mitochondrial disease in humans. In this study, the authors reported that two sisters both had a homozygous mutation in SDHA (c.1684 C>T) and that both sisters developed Leigh's syndrome at 10 months of age. One died at 19 months and another was still alive at 13 months.

Exhibit 110 (Beatrice Parfait et al., Compound Heterozygous Mutations in the Flavoprotein Gene of the Respiratory Chain Complex II in a Patient with Leigh

Syndrome, 106 Human Genetics 246-43 (2000)) presents a case study of a child with Leigh's syndrome who, like Trystan, had a compound heterozygous mutation of her SDHA gene. The child in Parfait shared one of his two mutations with Trystan (c.1571 C>T). However, the other mutation was distinct between the two children. Little is known about the course of the disease for the young child presented in the Parfait article, other than that she presented with Leigh's syndrome at 9 months of age, demonstrating psychomotor delays and cerebellar ataxia. The authors in the Parfait article took the additional step of showing that the reduced functioning of the young child's SDH protein was attributable to the c.1571C>T mutation (the mutation Trystan had), confirming the mutation's pathogenicity.

Exhibit 94 (Rudy Van Coster et al., Homozygous Gly555Glu Mutation in the Nuclear-Encoded 70 kDa Flavoprotein Gene Causes Instability of the Respiratory Chain Complex II, 120A Am. J. Medical Genetics 13-18 (2003)) presents the case study of a young child with a homozygous mutation in the SDHA gene (c.1664 G>A) whose symptoms developed at five months of age and then died two weeks later following a respiratory infection. Though the child may have had Leigh's syndrome, she "died in infancy before any sign of Leigh syndrome could develop." Id. at 4.

Exhibit H, tab 28 (R. Horvath et al., Leigh Syndrome Cased by Mutations in the Flavoprotein (Fp) Subunit of Succinate Dehydrogenase (SDHA), 77 J. Neurology Neurosurgery Psychiatry 74-76 (2006) presents the case of a young girl with a compound heterozygous mutation in her SDHA gene. Her two mutations were not seen in any other study. The patient first showed signs of Leigh's syndrome at five-months of age. While she had reached 10 years at the time the study was published, she had also shown an arrest of her psychomotor development and experienced recurrent seizures.

Exhibit H, tab 27 (Alistair T. Pagnamenta et al., Phenotypic Variability of Mitochondrial Disease Caused by a Nuclear Mutation in Complex II, 89 Molecular Genetics and Metabolism 214-21 (2006)) presents the case of a young boy with the exact same mutations presented in exhibit 94 (Van Coster). However, in contrast to the patient described in Van Coster, the patient in Pagnamenta did not develop symptoms of Leigh's syndrome until 22 months of age. While his onset was rapid, he began showing an improved clinical picture after turning four. At the time the article was published, the child was 10 years old and showed variably impaired motor function, but did not appear to manifest any cognitive deficits and attended a mainstream school.

Exhibit 79 (Aviva Levitas et al., Familial Neonatal Isolated Cardiomyopathy Caused by a Mutation in the Flavoprotein Subunit of Succinate Dehydrogenase, 18 European J. Human Genetics 1160-65 (2010)) is the most recently published article in the record concerning the significance of SDHA mutations. The Levitas article is unique for two reasons. First, the authors presented an examination of fifteen individuals from two large consanguineous families, allowing for better discrimination about the penetrance of the mutation. Second, the patients did not present with Leigh's syndrome. Instead, with the exception of one patient, the subjects had, or had died of, cardiomyopathies of various severities. The onset of the disease, or death, occurred at earlier than one year of age in all the children studied. This is all the more fascinating because the mutation involved in Levitas was the same exact mutation that was associated with Leigh's syndrome in Van Coster and Pagnamenta. Nonetheless, not a single family member developed Leigh's syndrome. Even more, at least one patient, the father, who had the homozygous mutation that was also present in Van Coster and Pagnamenta (c.1664 G>A), had no symptoms of disease at all. This astonished the researchers and they performed several follow-up studies to try to explain this finding, though they had no success. Importantly, it was confirmed that this patient had a loss of function of the SDH gene, much as was the case in Parfait, but nonetheless did not develop any disease.

3. The Secretary's Argument Regarding Trystan's Clinical Course

In his brief, the Secretary took the position that Trystan's clinical course was set in stone due to his genetic mutation: "respondent's position [is] that the current scientific evidence demonstrates that Trystan was nearly certainly destined to develop Leigh's syndrome due to his preexisting SDHA gene mutations." Resp't's Preh'g Br. at 15.

The Secretary's pre-hearing brief argued that the determination that Trystan's mutations were pathogenic was sufficient to conclude that Trystan was destined to develop Leigh's syndrome. To support this syllogism, he cited the ACMG guidelines, a source on which both parties relied.

> The ACMG proposed that the term "likely pathogenic" be used to mean "greater than 90% certainty" that the variant is "disease-causing." Respondent recognizes that the chance Trystan developing Leigh syndrome may not be 100%. . . . Nonetheless, Trystan's mutations are "pathogenic." If his mutations were classified as the lesser "likely pathogenic," it would mean that based on an evaluation of all currently available scientific evidence, there is a greater than

> 90% chance that they would cause disease. In sum, the ACMG Guidelines support respondent's position that the current scientific evidence demonstrates that Trystan was nearly certainly destined to develop Leigh's syndrome due to his preexisting SDHA gene mutations. Petitioners' argument that the vaccine in any way altered Trystan's actual clinical course is entirely speculation.

Resp't's Preh'g Br. at 14-15 (citing exhibit J (Richards) at 11-16).

Dr. Raymond saw the evidence differently from the Secretary. Dr. Raymond did not argue that the "pathogenic" label was, itself, sufficient to conclude that there was 90% or greater certainty that Trystan would develop Leigh's syndrome based on the mutation. Instead, Dr. Raymond referenced his "clinical genetic analysis" to conclude that the mutation was 100% penetrant. Tr. 900. More specifically, he said that his opinion was "based upon the information that we have on the functional consequences of these two alterations seen in Trystan, as well as based upon the prior clinical experience in Parfait, that this will result in Leigh's syndrome." Id. (referencing exhibit 110 (Parfait)). The Parfait article, and its significance, is discussed in more detail, below.

4. The Sanchezes' Argument Regarding Trystan's Clinical Course

The Sanchezes did not dispute that Trystan possessed two pathogenic mutations in his SDHA gene, mutations that caused his SDH protein to not function quite correctly. Pet'rs' Preh'g Br. at 28-29 ("Trystan has two identified mutations in his SDHA gene, which regulates mitochondrial cellular energy metabolism. These mutations are pathogenic variants"); see also Tr. 974 (Dr. Niyazov stating "I do not dispute pathogenicity of that mutation, I do not, because this is a pathogenic mutation"). Instead, the Sanchezes argue something happened to Trystan that caused his disease to manifest, resulting in his current pathology. Pet'rs' Preh'g Br. at 23. The Sanchezes' argument that Trystan was okay until he wasn't—despite possessing a pathogenic mutation for his entire existence—is consistent with the medical literature of other mitochondrial disorders as well as the well-accepted fact that onset of Leigh's syndrome usually occurs during or following an intercurrent infection. See exhibit 148 (Rahman); see also section, V.A, above. These sudden turns for the worse, as reviewed above, are referred to as decompensating events.

Accordingly, the Sanchezes argue that but for the vaccination, Trystan would never had turned for the worse or that he would have done so far later in life. Because later onsets of Leigh's syndrome are associated with better outcomes, a later onset could be significant. See exhibit 97 (Kalliopi Sofou et al.,

A Multicenter Study on Leigh Syndrome: Disease Course and Predictors of Survival, 9 Orphanet Journal of Rare Diseases 52 (2014)) at 5. Dr. Steinman stated that we might have expected Trystan's onset of Leigh's syndrome to have occurred between 8 and 16 years old. Tr. 350. Dr. Niyazov, on the other hand, opined that more likely than not, Trystan would not have developed Leigh's syndrome. Tr. 509.

Dr. Steinman's argument is founded on Pinard et al. Exhibit 98 (J.M. Pinard, Syndrome de Leigh et Leucodystrophie par Deficit Partiel en Succinate Deshydrogenase: Regression sous Riboflavin, 6 Archives Pediatrics 421-26 (1999)).[21] In Pinard, the child had Leigh's syndrome and presented with severe neurological features at 10 months of age, but then ultimately developed only moderate psychomotor developmental delays by the age of five. Dr. Steinman testified that the mutation in Pinard was the "closest" he could get to Trystan's mutation. Tr. 335.

As for Dr. Niyazov, he stated that he based his conclusion that Trystan would *not* have, more likely than not, developed Leigh's syndrome—despite his genetic mutation—on exhibit 79 (Levitas). Dr. Niyazov stated his argument thusly:

> THE WITNESS: More likely than not, he would not have developed Leigh's, and can I explain why?
>
> SPECIAL MASTER MORAN: Yes.
>
> THE WITNESS: Based on the SDHA mutation that causes Leigh's, he had less likelihood of developing Leigh's based on the literature that I've provided, which 15 people who did not develop Leigh's in Levitas' article are more than any other SDHA related Leigh's ever reported to my knowledge. It's more than 50 percent there for no, not -- it's more likely than not he would not have developed it, and I'm talking about SDHA, not Leigh's in general.

Tr. 509 (referencing exhibit 79 (Levitas)).

5. Resolution of Genetic Cause

The question of Trystan's clinical genetic course is an incredibly complex part of what is already a complex case. Little is known with certainty, which partly

[21] An English translation of this article was entered as exhibit 100.

explains how the experts in these cases can be so far apart. For the purpose of this analysis, the undersigned has divided the arguments into three parts. First, does the uncontested fact that Trystan had pathogenic mutations make Trystan's genetic course certain? Second, was Trystan more likely than not going to develop a severe mitochondrial disorder in his lifetime? Third, was the course of this disorder or severity of this disorder predictable on a more likely than not basis?

a) The Significance of the Fact that Trystan's Mutations were Pathogenic

As noted above, the Secretary argued that the ACMG guidelines for what is and is not a pathogenic mutation dictates that because Trystan had a pathogenic mutation, there was, at least, a 90% chance that Trystan would develop Leigh's syndrome.

However, the Secretary's argument presented in his pre-hearing brief ignored the distinction between the concepts of pathogenicity and penetrance / expressivity. While there is not debate that Trystan's mutations are pathogenic, a pathogenic genotype does not necessarily guarantee a specific phenotype due to the phenomena of incomplete penetrance and variable expressivity. See section V.C.1, above. This distinction between pathogenicity and penetrance / expressivity constituted a central part of Dr. Niyazov's opinion. See Tr. 462–96.

To be sure, the ACMG—which the Secretary cites for his conclusion that pathogenic means that a mutation *will* cause a disease—also acknowledges the importance of considering penetrance and expressivity and draws a clear distinction between pathogenicity determinations and forward-looking conclusions about a disease course based on the presence of a mutation alone. In fact, the ACMG expressly disclaims the use of its pathogenicity criterion in making claims about a patient's future course. This express disclaimer occurs just pages after the Secretary's heavily cited passage:

> Caution must be exercised when using these guidelines to evaluate variants in healthy or asymptomatic individuals or to interpret incidental findings unrelated to the primary indication for testing. In these cases the likelihood of any identified variant being pathogenic may be far less than when performing disease-targeted testing. As such, the required evidence to call a variant pathogenic should be higher, and extra caution should be exercised. In addition, the predicted penetrance of pathogenic variants found in the absence of a phenotype or family history may be far less than predicted based on historical data from patients ascertained as having disease.

Exhibit J (Richards) at 15. Thus, the ACMG guidelines for pathogenicity are based on disease-targeted testing. In other words, testing that looks back at the genome after the disease has already been identified in order to see if there is an identifiable genetic cause. As noted in the text above, the probability that a genetic mutation will actually cause a disease in a healthy or asymptomatic individual (e.g., Trystan before the vaccination) "may be far less." How much less is hard to tell. Unfortunately, the experts did not address this paragraph of the ACMG guidelines.

Ultimately, even the Secretary's own genetics expert acknowledged that the very fact that a mutation is pathogenic does not guarantee, or even make more likely than not, a certain disease course. When the undersigned asked Dr. Raymond how a mutation to the BRCA1 gene would be classified under the ACMG guidelines—considering the fact that the mutation increases the risk for breast and ovarian cancer, but does not make development of those cancers certain—Dr. Raymond acknowledged that it would be a pathogenic mutation, but not completely penetrant. Tr. 1005-06. Accordingly, the simple argument that because Trystan's mutation was pathogenic, his disease course was "destined," must be rejected.

b) Penetrance of Trystan's Mutations

Although the Sanchezes persuasively argued that pathogenicity did not mean that a mutation will certainly cause a disease, the evidence in the record indicates that a mutation that causes loss of function in the SDH enzyme will eventually manifest as a life-altering mitochondrial disease.

As noted before, the Secretary emphasizes the results from Parfait et al. However, Dr. Raymond's conclusion of 100% penetrance does not obviously follow from the Parfait article alone. While exhibit 110 (Parfait) presents the closest case of a mutation similar to Trystan, it is limited by two important factors. First, though both Trystan and the child in Parfait had two mutations, the children only shared one of the mutations. This makes it difficult to account for the effect of the second, non-shared, mutation on each child's disease course. Second, the Parfait article (and Trystan's own course, for that matter) only represents a single data point. Case studies, by their nature, do not lend themselves to inferences about the penetrance of a mutation. This is for, at least, two major reasons. First, case studies do not draw from a large enough sample to provide meaningful inferences about the general population. Second, case studies present no epidemiological value due to the inherent ascertainment bias (i.e., case studies are not written about individuals with the mutation that are asymptomatic).

However, Parfait was not the only article in the record that discussed the prognosis for individuals with pathogenic SDHA mutations. As reviewed above, the results from Bourgeron, Parfait, Van Coster, Horvath, and Pagnamenta all stand for the proposition that pathogenic mutations of the SDHA gene are associated with causing Leigh's syndrome. As summarized by the most recently published article, "Pathogenic mutations in the SDHA gene have rarely been documented in children, and all but one case have been reported in patients with Leigh's syndrome." Exhibit 79 (Levitas) at 2. However, each of these case reports face the same ascertainment bias that Parfait suffered. These studies do not tell us about those individuals with SDHA mutations that do not manifest a disease. Because of the rarity of SDHA mutations, it is difficult or impossible to know about these individuals.

This concern about ascertainment biases underlined much of Dr. Niyazov's argument. The essence of his argument was that individuals with Trystan's same mutations—or other mutations that cause loss of function of the SDH enzyme—can live with no sign of disease. And, because they have no sign of disease, they are not genetically tested and thus their mutations remain unknown. See Tr. 1003-04. In support of this conclusion, Dr. Niyazov relied directly on exhibit 79 (Levitas):

> Q So was it your testimony that there are people walking around that have Trystan's SDHA gene mutations that are normal?
>
> A Yes, that's what the Levitas article showed.

Tr. 509-10. However, Dr. Niyazov's reliance on exhibit 79 (Levitas) to show that Trystan could have developed normally appears misplaced insofar as the logic ultimately weighs against the Sanchezes' argument.

The experts debate the extent to which comparisons can be drawn between the different SDHA mutations in the different articles. For Dr. Niyazov's argument here, he presumes that we can meaningfully apply the findings from exhibit 79 (Levitas) to someone with Trystan's specific mutations to his SDHA gene. That may or may not be true. However, if it is true, the outlook for someone with Trystan's mutations is very poor. While the children in exhibit 79 (Levitas) did not develop Leigh's syndrome, all but one developed a life-altering mitochondrial disease.

Of course, Dr. Niyazov is correct in pointing out that the father in exhibit 79 (Levitas) had the homozygous mutation and the loss of function in his SDH protein but was, by all appearances, healthy. This, as the authors point out, escapes explanation. However, it represents a curious case and a reminder of the

complexity of clinical genetics. It does not constitute the norm or what can be expected.

As with most in medicine, very few things are certain. But, on balance, the evidence favors the conclusion that, for all practical purposes, Dr. Raymond's genetic analysis is correct that Trystan's mutations could be expected to be at least close to 100% penetrant.

c) Variable Expressivity of Trystan's Mutations

While the evidence favors that Trystan's SDHA mutations were nearly certainly going to manifest as a serious mitochondrial disease, the record demonstrates that there is substantial room for variable expressivity for mutations to SDHA. As a result, the Secretary's argument that there was a set course for Trystan's disease cannot be credited entirely.

The variable expressivity of SDHA mutations is easily demonstrated by a comparison of exhibit 94 (Van Coster), exhibit H, tab 27 (Pagnamenta), and exhibit 79 (Levitas). All involve individuals with the same homozygous mutations to c1664 of the SDHA gene. Despite this, as reviewed above, the variations in the clinical course of the patients differ markedly.

The Secretary argues that the variable expressivity of the c1664 mutation is irrelevant since Trystan had a different mutation in his SDHA gene. See Tr. 908-09. However, the Secretary did not adequately explain why one loss-of-function mutation to the SDHA gene would have extreme variable expressivity while another would have none at all. It may be true that this is the case, but the evidence in the record does not appear to support that conclusion. Instead, the record does support the idea that "environmental factors, such as infection . . . or other metabolic stress may have contributed to the observed difference in phenotypes between these two patients." Exhibit 83 (Pagnamenta) at 7.

Though the Sanchezes' position that SDHA mutations are variably expressive must be credited, their argument regarding Trystan's expected clinical genetic course was not persuasive. Dr. Steinman's argument of an onset between ages 8 and 16 was based on the case of a single case study, exhibit 98 (Pinard). However, this case study did not appear to reflect the typical expected progression that was presented in the literature. Furthermore, Dr. Steinman's argument that the case study in Pinard was the "closest" genetic match to Trystan's condition did not make sense since the patient in Pinard did not have his genome sequenced and thus the locus of his mutation, even whether it was a SDHA mutation at all, is unknown. At the same time, Parfait presents a patient with one of Trystan's exact

mutations and yet Dr. Steinman does not reference it at all in his opinion on the expected clinical course.

Dr. Niyazov's testimony regarding Trystan's expected course was even less persuasive. He argued that Trystan, more likely than not, would never even had developed Leigh's syndrome, citing exhibit 79 (Levitas). To the extent that the mutation in exhibit 79 (Levitas) can be extended to Trystan's mutations, the article also showed that two-thirds of children with the mutation died before the age of one. Exhibit 79 (Levitas) at 6. Though it may be true that the children were never diagnosed with Leigh's syndrome, it is also true that their progression was considerably worse than Trystan's. Dr. Niyazov cannot point to exhibit 79 (Levitas) for the proposition that Trystan would not have developed Leigh's syndrome while also ignoring the tragic fate of the vast majority of children in that study.

In contrast, the Secretary's argument that Trystan's clinical course is entirely consistent with what is known about SDHA mutations is persuasive and must be credited based on the evidence. Trystan's progression, by all means, appears typical, if not better, than what would be expected for an individual with a pathogenic mutation to his SDHA gene. Compare exhibit 97 (Sofou), exhibit H tab 7 (Bourgeron), exhibit 110 (Parfait), exhibit 94 (Van Coster), exhibit H tab 26 (Horvath), and exhibit 83 (Pagnamenta) with exhibit 140 at 6 (Dr. Haas, Trystan's treating physician and an expert in mitochondrial disorders, noting that "Trystan's phenotype does not appear to be as severe as he is still able to feed himself at age 6").

6. Genetics Summary

As noted previously, this decision does not rest on a finding as to what Trystan's expected phenotype was based on his genetic mutation. This is for the very fact that this decision ultimately concludes that preponderant evidence does not exist to show that Trystan's course was affected by the vaccination.

For the purpose of preserving the record, the undersigned has examined the evidence presented by the parties regarding the significance of Trystan's genetic mutations on his expected clinical course. The undersigned finds that the Secretary provided persuasive evidence to show that Trystan's mutations were expected to cause serious mitochondrial disease. While the undersigned finds that the type and course of the mitochondrial disease is extremely variable and allows for worse outcomes to be potentially attributable to environmental factors—such as a response to a vaccination—the evidence nonetheless supports the Secretary's

position that Trystan's actual course is entirely consistent with what is known about his genetic mutations.

VI. Conclusion

While the Sanchezes presented sufficient evidence to indicate that Trystan's vaccinations could cause the manifestation of Leigh's syndrome, the evidence does not support the conclusion that this is what happened to Trystan. Accordingly, the Sanchezes claim for compensation is DENIED.

The Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

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