In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 14-65V

(to be published)

HEIDI SHARPE, *as legal representative of her minor child,* L.M.,	*	Special Master Corcoran
Petitioner,	*	Filed: November 5, 2018
v.	*	Diptheria-Tetanus-Acellular Pertussis ("DTaP") Vaccine; DYNC1H1 Mutation; Significant Aggravation; Encephalopathy.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Curtis Webb, Twin Falls, ID, for Petitioner.

Amy Kokot, U.S. Dep't of Justice, Washington, DC, for Respondent.

ENTITLEMENT DECISION[1]

Heidi Sharpe, as legal representative of her child, L.M., filed a petition on January 27, 2014, seeking compensation under the National Vaccine Injury Compensation Program ("Vaccine Program").[2] Pet. at 1, ECF No. 1. In her petition, Ms. Sharpe alleged that the diphtheria-tetanus-acellular pertussis ("DTaP") and other vaccinations administered to L.M. on February 10, 2011, caused L.M. to suffer: (1) a Table injury in which her underlying brain malformation/white matter deficiency/other genetic mutation constituted an encephalopathy that was significantly aggravated

[1] This Decision will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire Decision will be available in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10–34 (2012) (hereinafter "Vaccine Act" or "the Act"). Individual section references hereafter shall refer to § 300aa of the Act.

by the DTaP vaccine, and/or (2) an off-Table injury resulting from the February 10th vaccines she received significantly aggravating the same constellation of underlying conditions. *Id.* at 2.

An entitlement hearing was held in this matter on March 13–14, 2018. For the reasons stated in more detail below, I hereby DENY an award of damages in this case. Because it was incontrovertibly demonstrated that L.M. possessed a genetic mutation associated with the seizures/spasms disorder she was diagnosed with after vaccination, the success of Petitioner's claim turned on whether the vaccines L.M. received significantly aggravated the sequelae of that mutation. But Petitioner did not successfully establish that the vaccines did so (or that they *could* specifically worsen the expected course of an individual with the precise mutation possessed by L.M.). Petitioner's alternative Table claim of significant aggravation of a preexisting "encephalopathy" also failed, because it relied on a legally untenable construction of the relevant portions of that Table claim's definitions.

I. Factual Background

Pre-Vaccination History

L.M. was born at term on July 26, 2010. Ex. 1 at 5. At six months of age (and prior to her February 10, 2011 vaccinations), her development, motor skills, and responsiveness were deemed normal. Ex. 2 at 6. Her parents have also confirmed in witness statements that her overall development was normal at this point, and that she seemed a healthy and happy baby. *See, e.g.*, Ex. 12 at 2 (affidavit of Richard Moore, L.M.'s father). Prior to this time, L.M. had received several childhood vaccines—Pediarix (DTaP, hepatitis B, and inactivated polio), haemophilus influenzae type B, pneumococcal conjugate, and rotavirus—on two occasions (her two-month well-child visit on September 20, 2010, and her next well-child evaluation on November 18, 2010) without incident. Ex. 1 at 100–01, Ex. 2 at 4–5, 30.

At a January 17, 2011 well-child visit, Petitioner informed L.M.'s pediatrician that L.M. had developed symptoms of an upper respiratory infection ("URI")[3] and a rash; she was diagnosed with a viral exanthema,[4] but was otherwise deemed healthy. Ex. 2 at 6. Vaccinations that were scheduled to be given at this time were postponed due to her illness. *Id.* at 7. The next day, Ms. Sharpe brought L.M. to Central Montana Medical Center's emergency room in Lewistown, Montana, reporting "inconsolable crying" for one hour after leaving L.M. under the care of Petitioner's thirteen-year-old daughter, although her exam was normal. Ex. 3 at 8. Two weeks

[3] This record also states that Ms. Sharpe "took [L.M.] to [the] ER 2 days ago. Dx'd with [v]iral URI." Ex. 2 at 6. The filed medical records, however, do not document a January 15, 2011 ER visit. *See, e.g.*, Ex. 3 at 1–2; Ex. 4 at 1 (listing L.M.'s emergency room visits and hospital admissions).

[4] A disease featuring prominent skin eruptions or rashes. *Dorland's Illustrated Medical Dictionary* 656 (32nd ed. 2012) (hereinafter "*Dorland's*").

later, in early February 2011, Petitioner brought L.M. to her pediatrician's office with complaints of congestion and "thick green nasal drainage for [six] weeks." Ex. 2 at 8. L.M. was diagnosed with congestion and received an antibiotic. *Id.*

February 2011 Vaccinations and Alleged Reaction

At about 4:00 pm on February 10, 2011, L.M. received another dose of Pediarix, plus the ActHIB (HIB) and Prevnar (Pneumococcal Conjugate) vaccines. Ex. 2 at 30. By 7:00 pm that evening, Petitioner purports, L.M. had developed a fever and became flushed and floppy. Ex. 11 at 3 (affidavit of Ms. Sharpe). The next day, Ms. Sharpe phoned L.M.'s pediatrician, Dr. Annette Comes, and (consistent with her affidavit) reported that after vaccination, L.M. had "developed a fever and [was] whimpery [and] wak[ing] up 'screaming.'" Ex. 2 at 19. Petitioner specifically observed that L.M. had not reacted to the vaccines she had received the prior fall. *Id*; *see also* Ex. 11 at 3. L.M.'s doctor proposed "that this [was] most likely not related to the injections," and attributed L.M.'s symptoms to a possible viral illness (also consistent with the medical record, given what Petitioner reported to pediatricians less than two weeks before). Ex. 2 at 19. Petitioner was instructed to administer alternating doses of ibuprofen and Tylenol, and to bring L.M. in for a doctor's visit the following Monday (February 14, 2011) if she did not appear to improve. *Id.*

Ms. Sharpe contends that L.M. did not improve that weekend, but continued to run a high fever and to display floppiness and an uncharacteristic disinterestedness. Ex. 11 at 4. She avers that she thereafter called the ER twice about her concerns, but was rebuffed (*id.* at 4)—although no records confirm these calls. *See* Ex. 74 at 17–18 (no calls from Ms. Sharpe to ER on February 12 or 13). On February 15, 2011, however, Petitioner brought L.M. to the ER, reporting that L.M. had "suddenly become 'stiff all over' [and] unresponsive" after an episode lasting approximately thirty seconds. Ex. 3 at 13.

During that episode, L.M. had no fever or other identifiable URI symptoms. Ex. 3 at 13. The record from this visit notes that L.M. had experienced a fever related to the vaccinations from four days prior, but downplays the extent to which Petitioner at the time associated L.M.'s prior illness with her presenting condition. *See id.* The record from this visit also reveals that Petitioner reported to treaters at this time that the month before (January 2011) L.M. had similarly experienced an "unexplained episode of sudden flaccidity [and] unresponsiveness" for approximately thirty seconds, followed by several minutes of crying and irritability. *Id.* at 13. L.M.'s temperature at the ER was 97.5 degrees Fahrenheit, she was alert and playful, and although a "bit listless," she displayed few other alarming clinical symptoms. *Id.* at 12–14. However, L.M. was also noted to have "floppy" motor control and skills, poor head control, and "pupils that were equal and reactive bilaterally." *Id.* at 16.

The afternoon of February 15th, L.M. had a second seizure event at 3:30 pm. Ex. 3 at 18. A nurse observed L.M. to be "staring off into space" and unresponsive to touch or grasp. *Id.* At this point, Dr. Comes contacted St. Vincent Hospital in Billings, Montana, to arrange L.M.'s transfer, after noting that her unresponsiveness and listlessness could indicate a possible seizure. Ex. 4 at 7; Ex. 13 at 18. That evening, L.M. was transferred to St. Vincent via ambulance, and records from her admission suggest that EMTs detected an additional episode of tonic stiffening as they prepared to effect the transfer. Ex. 4 at 3, 5. Upon arrival at St. Vincent, the admitting physician noted that L.M. had been well "until about a month ago," when episodes in which she "blanked out" were first observed, along with head bobbing and eye crossing. *Id.* at 3. The history from this initial record also notes that after L.M. was brought to the ER in Lewistown, she would "not focus or track except briefly and mainly then only to the left," and the initial assessment expressed uncertainty as to whether L.M.'s condition was the product of seizures, sleepiness, or the phenobarbital she had received just before being transferred to St. Vincent. *Id.* at 3–4.

St. Vincent had a larger neurologic evaluating staff and better facilities than Central Montana Medical Center, and L.M. there received a neurologic work-up the next day (February 16, 2011). The pediatric neurologist who saw L.M., Dr. Tarif Bakdash, confirmed in his intake history that she had experienced three seizures in the last twenty-four hours, and that the third had features resembling infantile spasms. Ex. 4 at 5. But that same record also characterized L.M. as "being hypotonic or floppy" since birth, and noted a history of gastroesophageal reflux disease ("GERD"). *Id.* Petitioner also informed Dr. Bakdash of L.M.'s two-day fever after vaccination, but added that "a few days later she was fine." *Id.* Dr. Bakdash's neurologic exam noted that L.M.'s reflexes were "one out of four," and that she was "hypotonic throughout." *Id.* at 6. His initial impression was that L.M. was suffering from "generalized seizure pattern and infantile spasms." *Id.* Dr. Bakdash expressed his preliminary assessment that L.M. could likely be discharged shortly, although he ordered some additional testing for confirmation of his views. *Id.*

The next day, February 16, 2011, L.M. received a magnetic resonance imaging ("MRI") of her brain, performed without contrast,[5] with three different imaging sequences performed. Ex. 5 at 3; *see generally* Ex. 69.[6] The radiologist responsible for the MRI observed "no evidence of migrational abnormality," no "acute ischemia or infarction," typical brain parenchyma, and

[5] When an MRI is performed with contrast, a dye containing gadolinium is intravenously injected into the body. This dye can help enhance certain details in MRI images, including disruption of the blood-brain barrier and the age of brain lesions. Mayo Clinic, *MRI*, https://www mayoclinic.org/tests-procedures/mri/about/pac-20384768; *Bender v. Sec'y of Health & Human Servs.*, No. 11-693V, 2018 WL 3679637, at 2* n.6 (Fed. Cl. Spec. Mstr. July 2, 2018).

[6] Specifically, the following imaging sequences were performed: a sagittal spin echo T1; an axial T2 with diffusion weighted images; and a coronal FLAIR. Ex. 5 at 3. Axial images show transverse or (horizontal) "slices;" sagittal images run vertically (perpendicular to axial images) and show a lateral view; and coronal images show a frontal vertical perspective. University of Wisconsin School of Medicine and Public Health—Department of Radiology, *Neuroradiology Learning Module—Imaging Techniques: The Basics*, https://sites.google.com/a/wisc.edu/neuroradiology/image-acquisition/the-basics (2011).

nothing else alarming, deeming the overall results "unremarkable." Ex. 5 at 3. The overall normal and unremarkable character of this MRI was confirmed on L.M.'s discharge. *Id.* at 7.

Treaters also performed an electroencephalogram ("EEG") for L.M. on February 16th, however, which revealed hypsarrhythmia,[7] a primary clinical characteristic of infantile spasms. Ex. 4 at 9. This confirmed Dr. Bakdash's initial impression that infantile spasms/West syndrome was the proper diagnosis, and he maintained the phenobarbital treatments initiated for L.M. right before her arrival at St. Vincent. *Id.* at 7–8. L.M. experienced no additional seizures at St. Vincent, and was discharged on February 17th. *Id.* The discharge summary records Petitioner's earlier-referenced recollection that L.M. had previously experienced episodes of "'spacing out' when she would have a strange look on her face and seemed unresponsive," although the record does not specify when. *Id*.

By the time of discharge, L.M. had returned to her pre-hospitalization baseline (with some generalized hypotonia). Ex. 4 at 8. However, she was taken back to the ER at Central Montana Medical Center in Lewistown on March 21, 2011, with complaints of ongoing seizures and URI symptoms. Ex. 3 at 56–57. The treater's impression was that L.M. was "somewhat floppy" with "loose muscle tone" and continued to have five to six seizures daily but otherwise showed "[n]o other obvious abnormalities." Ex. 3 at 57.

L.M.'s Health After Infantile Spasms Diagnosis

L.M.'s subsequent medical history documents significant developmental difficulties in the course of dealing with her West syndrome symptoms. Dr. Comes's notes from February 21, 2011 post-hospitalization follow-up visit, for example, show that L.M. had "poor eye contact" and "poor head control." Ex. 2 at 10. Dr. Comes made similar observations at an April 11, 2011 visit, when she noted that L.M.'s eyes "don't really focus on anything," that she had "[n]o interactive smile," and that she "really didn't have good head control at all." *Id.* at 14. A physical therapist's assessment from March 15, 2011, echoed such findings, describing L.M.'s poor muscle tone and difficulties holding up her head. Ex. 13 at 3–4.

Around this time period, L.M. was seen by Dr. Bakdash on several occasions. *See, e.g.*, Ex. 7 at 1–8. A follow-up EEG performed on April 18, 2011, confirmed her hypsarrhythmia, as well as new onset seizure activity in the left temporal region, for which L.M. was prescribed Keppra. *Id*. at 4–5. Dr. Bakdash's assessments in this period did not always corroborate Petitioner's assertions of post-vaccination progressive developmental decline. For example, a February 22, 2011 record noted that L.M. did "reach out for things," that she held her head up when placed on her stomach, and that she was "looking at things and tracking them." Ex. 7 at 2.

[7] "An electro-encephalographic abnormality sometimes observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas." *Dorland's* at 908.

He later noted L.M.'s persistent developmental delays and motor limitations (s*ee, e.g.*, Ex. 7 at 4), but overall seems to have viewed her delay as "static in nature" rather than progressive. *Id.* at 6 (July 12, 2011), 8 (November 8, 2011), 11 (March 14, 2012).

As of November 8, 2011, Dr. Bakdash's differential diagnosis for L.M. continued to include infantile spasms, complex partial seizures, and global developmental delay. Ex. 7 at 8. Other specialists evaluating L.M. that year proposed other explanations for her symptoms. For example, on October 27, 2011, Laura Nicholson, M.D., a developmental and behavioral pediatrician, diagnosed L.M. with static encephalopathy with epilepsy. Ex. 10 at 355–58. Based upon an examination of L.M. and a review of her history, Dr. Nicholson concluded that L.M.'s condition appeared metabolic, "with a sudden onset with the stress of the six month shots, recurrent regression with illness . . . [i]t looks like a mitochondrial disorder . . . but the initial labs do not show acidosis." *Id*. at 357–58. In an e-mail to Samuel P. Yang, M.D., a geneticist, Dr. Nicholson stated that L.M. "was fine until six months of age and then became neurologically devastated after a fever with her six-month shots. She has infantile spasms, extreme hypotonia, [and] severe neurological regression." *Id*. at 80.

Dr. Yang thereafter examined L.M. on December 8, 2011. Ex. 10 at 13–15. The history from this visit states that "[c]oncern developed around the time [L.M.] was six months old following an illness and vaccinations when she became 'hypotonic and hot.'" *Id*. at 13. Dr. Yang observed that although L.M.'s EEG was consistent with infantile spasms, her clinical picture and lack of response to steroids were "more typical for complex partial seizures." *Id*. at 14. He proposed that L.M. might have a cerebral folate deficiency, and recommended treatments aimed at addressing the deficiency. *Id*. at 14–15.

L.M. had improved by March 14, 2012, when she next saw Dr. Bakdash. Ex. 7 at 11–12. In the wake of treating L.M.'s possible cerebral folate deficiency, her generalized seizures had ceased, and an EEG now showed no hypsarrhythmic changes—and Ms. Sharpe indicated that L.M. appeared to experience fewer seizures since the new treatment was initiated. *Id*. at 11. At that time, L.M. was receiving physical, occupational, and speech therapies. *Id*. On May 1, 2012, Dr. Yang noted that L.M.'s seizure frequency had "decreased dramatically," and that her infantile spasms occurred only once or twice per week. Ex. 10 at 19. Her diagnoses now included cerebral folate deficiency, infantile spasms, global developmental delay, and esotropia.[8] *Id.*

At present, L.M. continues to experience seizures and developmental delays. Petitioner alleges that, at 7 years and 5 months of age, L.M. can crawl, as well as walk with a walker when aided (someone needs to direct her and catch her if she stumbles). Tr. at 60–61. She takes the anticonvulsant Tegretol and a low dose of CBD oil (medical marijuana) to control her seizures. Tr. at 64. In her prehearing submission, Petitioner asserts that L.M. experiences "occasional

[8] Esotropia is a condition in which one eye deviates towards the other; in other words, the individual goes "cross-eyed." *Dorland's* at 648.

breakthrough seizures" even during periods of relatively good health, has a poorly coordinated grasp, suffers from cortical visual impairments, and is nonverbal, though she can use a few signs to express ideas such as "hungry," "thirsty," "I want," "yes," and "no." Pet'r's Pre-Hr'g Brief at 12, dated Dec. 12, 2017, ECF No. 73 ("Pet. Brief").

Evidence of Genetic Basis for Petitioner's Symptoms

Some time after this case's initiation, evidence potentially shedding light on the cause of L.M.'s seizures and related symptoms was uncovered. Specifically, on January 12, 2016, genetic testing performed by Ambry Genetics (a company that provides clinical diagnostics testing services for genetic diseases, including full exome sequencing) revealed that L.M. is "heterozygous for the alteration in the *DYNC1H1* [dynein cytoplasmic 1 heavy chain 1] gene [hereinafter, the "DYNC gene"]." Ex. 42 (ECF No. 54-1) at 37; *see also* Ex. R at 2, dated May 1, 2017, ECF No. 67-1 ("Descartes Rep.") (stating specifically that L.M. "is heterozygous for the alteration c.3278T>C (p.F1093S) in *DYNC1H1* in exon 13"). These records conclude that "[c]ollectively, the evidence supports the likelihood that the alteration in the *DYNC1H1* gene [hereinafter, the "DYNC mutation"] *is the cause of [L.M.'s] clinical symptoms*." Ex. 42 at 38 (emphasis added); *see also id.* at 40 ("[b]ased on the available evidence, the clinical overlap of this gene with [L.M.'s] reported phenotype is positive. [L.M.'s] overlapping features include infantile spasms, intellectual disability, ongoing refractory epilepsy, and diffuse hypotonia"). The Ambry Genetics report also references an unidentified "female patient" who Ambry Genetics had previously determined possessed the same mutation and had experienced a phenotypic outcome very similar to L.M.'s course. *Id.* at 41.

In the course of setting forth the above, the Ambry Genetics test results report includes a brief description of many items of literature reviewing the phenotypic outcomes associated with DYNC mutation variants. Ex. 42 at 39–40. It summarizes these studies by noting that "[n]o clear genotype-phenotype correlations have emerged, although alterations associated with malformations of cortical development tend to cluster in the motor domain, whereas alterations associated with SMA-LED [Spinal muscular atrophy with lower extremity predominance] tend to cluster in the stem domain." *Id.* at 40. Nevertheless, the Ambry Genetics results make note of reported occurrences that were inconsistent with the mutation's location as predictive of phenotype. *Id.*

On February 12, 2016, L.M.'s geneticist documented L.M.'s overall symptomatic condition as characterized by epilepsy, global developmental delay with absent speech, hypotonia, and mental retardation. *Id.* at 31–32.

II. Witness Testimony

A. Fact Witnesses

At hearing, both of L.M.'s parents—Ms. Sharpe and Richard Moore[9]—testified. *See* Tr. at 5–91. These two witnesses also provided affidavits (*see* Ex. 11; Ex. 12), and their testimony was largely consistent with their written statements.

1. *Ms. Sharpe*

Ms. Sharpe noted that L.M. had few problems early in her life, although she did suffer from GERD. Tr. at 6–7. The month before receiving the vaccines at issue, L.M. saw her pediatrician, where "nothing major" was noted. *Id.* at 9. Ms. Sharpe emphasized that L.M.'s development in January 2011 remained normal, and she seemed to be a happy baby. *Id.* at 10–11, 15. She also acknowledged that L.M. had a cold that January 2011 prior to receiving the vaccines, and received antibiotics for it, but noted that it was not accompanied by fever. *Id.* at 15–16.

Respondent questioned Ms. Sharpe about certain pre-vaccination records that could be construed as evidence of seizure-like activity. When asked about "episodes" of unresponsiveness mentioned in a February 15, 2011 record, Ms. Sharpe stated that she did not recall any such episodes.[10] Tr. at 12–13. When questioned later about the February 15th hospital visit notes, Ms. Sharpe again denied the accuracy of the record, stressing her view that L.M. had never had such seizures prior to vaccination. *Id.* at 69. She also denied informing treaters that L.M. had been floppy or hypotonic since her birth. *Id.* at 70.

Ms. Sharpe was also asked about the January 18, 2011 visit to Dr. Comes, when L.M. was described as crying inconsolably—a characterization Ms. Sharpe disputed. Tr. at 70–72. In her recollection, this visit was mainly attributable to an incident in which her older daughter had failed

[9] Many of the medical records refer to Mr. Moore as "Richard Hanson." *See, e.g.*, Ex. 4 at 2. As Mr. Moore explained at hearing, he was known by this name at the time of L.M.'s vaccination, but subsequently changed his name for personal reasons relating to his discovery of his biologic parent. Tr. at 74–75.

[10] Respondent's questions about possible episodes in January 2011 during which L.M. "became limp and unresponsive for about 30 seconds and then cried for several minutes" and "spaced out, had a strange look in her eyes and was unresponsive for several seconds" (Tr. at 12–13) seem to reference notes from Petitioner's February 15, 2011 ER visit, which reflect that, according to Ms. Sharpe, "a month ago [L.M.] had unexplained episode of sudden flaccidity [and] unresponsiveness for [about] 30 sec[onds], then crying [and] irritable for several minutes," as well as "a few other episodes of 'spacing out' where she had a strange look in her eye and was not responsive for several seconds." Ex. 3 at 13, 15.

to watch L.M. carefully while babysitting, and the behavior L.M. displayed was not, in Ms. Sharpe's view, comparable to L.M.'s later seizure activity. *Id.* at 72.

As Ms. Sharpe recalled, L.M. received the vaccines in question on the afternoon of February 10, 2011. Tr. at 17. Immediately after receiving the vaccines, L.M. cried and then quickly fell asleep, appearing flushed. *Id.* at 17–19. Later that afternoon toward evening she had trouble waking up and seemed feverish. *Id.* By 7:00 p.m., L.M. had a fever of 102 to 103 degrees Fahrenheit, and she was floppy and lethargic before falling asleep. *Id.* at 19–21.

Concerned about L.M.'s condition, Ms. Sharpe called Dr. Comes's office twice in the early hours of February 11, 2011. Tr. at 22–23. In particular, the pain relievers she was administering to L.M. were not effective in reducing her temperature, and L.M. was resistant to waking. *Id.* at 23, 25–26. Treaters, however, were dismissive of her concerns. *Id.* at 24. Ms. Sharpe called the pediatrician again at noon that day, informing the office that L.M. had woken up screaming and seemed uncomfortable and irritable—very different from how she had been before receiving vaccines the previous day—but the pediatrician's office again seemed not to deem L.M.'s condition significant, simply advising Ms. Sharpe simply to make an appointment to bring L.M. in on a later date. *Id.* at 26–29, 30–31.

Over the next few days, Ms. Sharpe testified, L.M. remained in a distressed condition. Tr. at 32. She did not, however, opt to bring L.M. in for a visit, maintaining that a nurse had made her feel that she was overreacting and that Dr. Comes's office was otherwise booked up. *Id.* at 33–34. On February 15, 2011, however, Ms. Sharpe observed L.M.'s head fall back and her body go stiff, with her color drained out, although she did not check L.M.'s temperature at this time. *Id.* at 34–35, 37. She then decided to take L.M. to the ER in Lewistown. *Id.* at 36. By the time they arrived, L.M. had begun to "come around," although she remained unresponsive and continued to resist waking. *Id.* at 38, 39–40, 46–47. At hearing, Petitioner expressed concerns about the quality of care L.M. received initially, and noted that after Mr. Moore arrived, he helped her press upon treating staff their shared view that L.M. should be transferred to a more up-to-date facility in Billings. *Id.* at 45–47, 49–50.

Ms. Sharpe testified that, prior to transfer, L.M. was administered an IV and drugs (treatment steps that Ms. Sharpe felt the ER had improperly failed to provide initially). Tr. at 50–51. During this period, L.M. remained unresponsive, resisted feeding, and would not hold up her head. *Id.* at 53–54. She was no better by the time they arrived in Billings that evening. *Id.* at 54. During the time L.M. was hospitalized at St. Vincent Hospital, Ms. Sharpe recalled, L.M. showed some improvement but was still "floppy," and experienced additional seizures despite medication. *Id.* at 57, 58–59.

Finally, Ms. Sharpe testified about L.M.'s current state of health. L.M. has trouble walking without assistance (especially outside of the home) and has a limited vocabulary, although her head control has improved. Tr. at 59–62. She also continues to experience seizures to varying degrees of severity, although medication helps control them. *Id.* at 63–64.

2. *Mr. Moore*

Mr. Moore testified that he worked on-site in the oil extraction industry in North Dakota at the time period relevant to this case, and was thus often away from the home he shared with Ms. Sharpe for several days at a time. Tr. at 75. He was in North Dakota around February 14–15, 2011, and had been there for several days. *Id.* at 76, 81. Prior to his departure for this shift, L.M. appeared to him a normal baby, who responded properly to her parents, had good head control, and could sit up. *Id.* at 77–79. He acknowledged that L.M. appeared to be developing a cold prior to his departure, but characterized it as nothing out of the ordinary. *Id.* at 80. Mr. Moore did not recall any instance prior to vaccination in which L.M. appeared unresponsive to him. *Id.*

Mr. Moore learned of L.M.'s post-vaccination problems while he was working away from home, after being contacted by Ms. Sharpe. Tr. at 81. He largely corroborated Ms. Sharpe's testimony about L.M.'s condition from February 11–15, 2011. *Id.* at 81–82. He was called while in North Dakota after Ms. Sharpe took L.M. to the ER in Lewistown, and immediately travelled back to Montana. *Id.* at 83–84. At the ER, Mr. Moore observed L.M. to be what he characterized as "catatonic" and nonresponsive, resisting any of his efforts to get her to react to his presence. *Id.* at 85–86.

Similar to Ms. Sharpe, Mr. Moore described his frustration arising from the perception that ER treaters were not adequately caring for L.M., and that more skilled neurologic expertise was required to ascertain the nature and cause of L.M.'s condition. Tr. at 86–87. Therefore, he and Ms. Sharpe concurred that L.M. needed to be transported to St. Vincent Hospital, and conveyed that request to ER treaters in Lewiston. After going to Billings, Mr. Moore indicated, L.M. appeared to him roughly the same as she had upon his arrival, and that since that time she has never returned to her pre-vaccination condition. *Id.* at 88.

B. Expert Witnesses

1. *Dr. Robert Shuman*

Dr. Shuman testified at hearing and prepared three written reports for Petitioner. *See* Ex. 17, ECF No. 16-1, dated October 2, 2014 ("Shuman First Rep."); Ex. 28, ECF No. 29-1, dated June 8, 2015 ("Shuman Second Rep."); Ex. 68, ECF No. 72-1, dated December 10, 2017 ("Shuman Third Rep."). Dr. Shuman overall opined that L.M. suffered from a preexisting, structural brain

deformity that, as a result of the vaccines she received, caused an interference in her brainstem activity that resulted in seizures. Tr. at 127.

Dr. Shuman is a pediatric neuropathologist with special expertise in child neurology. Tr. at 92–93. He received his M.D. from Stanford University. Ex. 19 at 1, ECF No. 16-3 ("Shuman CV"). He completed a residency in pediatrics at the University of Colorado, a residency in pathology at the University of Washington, and a residency in child neurology at the University of Kentucky. *Id.* At various points, he has served as a professor of neurology, neuropathology, and pediatric neuropathology at the University of Pittsburgh, the University of Nebraska, and the University of Oklahoma. *Id.* at 1–2; Tr. at 92–93. He is board certified in pathology, neuropathology, and child neurology, but not pediatrics. Tr. at 94; Shuman CV at 2.

Dr. Shuman acknowledged his particular interest in neuroimaging processes, like MRIs, stressing the degree to which this kind of testing had increased the reach of the field of pathology and revolutionized its capabilities. Tr. at 95. Because of his interest in such technological advancements, his career focus over time shifted to imaging instead of a clinical, patient-oriented practice. *Id.* at 96. Dr. Shuman possesses a certification from the American Society of Neuroimaging. *Id.* at 98. He retired from medical practice in 2006, and has not had a clinical practice since that time (and has therefore not had the occasion to review any MRIs for purposes of treatment, although he routinely views them in the context of serving as an expert—his primary source of income today). *Id.* at 97, 137, 139–40.

The core of Dr. Shuman's testimony and opinion was his interpretation of L.M.'s various MRIs, which he proposed demonstrated the existence and extent of an underlying encephalopathic condition. Overall, he stressed that (a) L.M. had a thin corpus callosum,[11] (b) L.M.'s ventricles were large and malformed, and (c) there were "irregular densities" in the white matter around the ventricles and under the cerebral cortex, all of which were suggestive to Dr. Shuman of a white matter disease of some kind or other cerebral malformation. Tr. at 101–02.

First, Dr. Shuman discussed the MRI obtained on February 16, 2011, after L.M. was taken to St. Vincent Hospital. *See* Ex. 69 at 2. This MRI is a sagittal image[12] showing the entirety of L.M.'s cranium, and in Dr. Shuman's interpretation evidenced the thin nature of L.M.'s corpus callosum. Tr. at 103, 105. The axial T2 image[13] obtained on the same date revealed that L.M.'s lateral ventricles were unevenly shaped—in particular, the left was shaped differently than the

[11] Corpus callosum is the "arched mass of white matter" located in the longitudinal fissure of the cerebrum. *Dorland's* at 417, 709, 711.

[12] *See supra* note 6.

[13] A T2 image, as distinguished from a T1 image, "excites water." Tr. at 106. Dr. Shuman explained that this shows the presence of cerebrospinal fluid. *Id.*

right, which appeared normal. *Id.* at 107–08. Dr. Shuman could not attribute this discrepancy solely to the positioning of the particular image. *Id.* at 107. His conclusion was that the ventricles, taken together, were overly large, asymmetric, and abnormal. *Id.* at 108.

In addition to such observations about structural deficiencies, Dr. Shuman reached other conclusions from these initial MRI images. He pointed out what he deemed striations in the white matter, which he deemed consistent with "perinatal teloleukoencephalopathy" ("PNTLE"), a white matter deficiency condition.[14] Tr. at 108–09. This alleged white matter deficiency he characterized as "part of the preexistent encephalopathy of [L.M.]'s genetic disease." *Id.* at 110. However, on cross-examination Dr. Shuman later admitted that this alleged white matter deficiency was not evidence of an acute brain injury (whether caused by a vaccine directly or by vaccine-induced epileptic activity), although he noted that an MRI would not reveal epileptic activity generally. *Id.* at 152.

Dr. Shuman next turned to the second set of MRI images, obtained in April 2011 (two months post-vaccination). Tr. at 110 (discussing Ex. 69 at 4). In his reading, these new images revealed "essentially no change in [L.M.]'s preexisting encephalopathic state," thus corroborating his interpretation of the initial images. *Id.* at 111. In fact, in Dr. Shuman's opinion, this set of images revealed the existence of a "static encephalopathy." *Id.* at 112. Finally, Dr. Shuman reviewed the third set of images, obtained on May 22, 2012 (over a year after the second set). *Id.* at 115 (discussing Ex. 69 at 6). He asserted that they were "pretty good" evidence of the structural abnormalities and white matter deficiencies that he maintained could be seen in the initial imaging sets, as well as the static nature of L.M.'s underlying encephalopathy. *Id.* at 115–16, 369.

Based on his review of these MRIs, Dr. Shuman opined (as mentioned above) that concurrent with L.M.'s purported structural deficiencies, she suffered from a specific kind of white matter deficiency: PNTLE. Tr. at 140. Dr. Shuman admitted, however, that the term was somewhat medically outdated and was subsumed within the concept of "white matter deficiency," although he stressed that PNTLE and white matter deficiency are "gradation[s] of the same disease." *Id.* at 141, 142, 162. He allowed that any PNTLE/white matter deficiency from which L.M. suffered was fairly mild, as corroborated by the MRI findings, and agreed that his interpretation of these MRI findings was not echoed by the radiologists who performed them. *Id.* at 143, 144, 162–63.

In advancing PNTLE as a reasonable diagnostic explanation for L.M.'s white matter deficiency, Dr. Shuman claimed there is support in the literature establishing that this condition/diagnosis is recognized, although his own personal experience also led him to propose it. Tr. at 141 (discussing J. Volpe, *Neurology of the Newborn* (4th ed. 2001), excerpts filed as Ex.

[14] Dr. Shuman defined a perinatal teloleukoencephalopathy as "a generalized insufficiency of the formation of white matter or the destruction of precursors of the white matter form cells" that leads to "blunting of the lateral ventricular angle [and . . .] dilatation of the lateral ventricle." Tr. at 109–10.

23, Ex. 26A, Ex. 26B (ECF Nos. 17-5; 17-8; 17-9); L. Woodward, et al., *Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants*, 355 New England J. Med. 685 (2006), filed as Ex. 25 (ECF No. 17-7)). He acknowledged, however, that the literature's reference to PNTLE did not precisely match or describe the PNTLE he observed from the MRIs. *Id.* at 141–42. In a similar vein, Dr. Shuman pointed to images from an article involving the effects of the DYNC mutation that he maintained were similar to what he observed in L.M.'s MRIs (and thus confirmed his overall view about the nature of her brain abnormalities). *Id.* at 116 (discussing M. Scoto, et al., *Novel Mutations Expand the Clinic Spectrum of DYNC1H1-Associated Spinal Muscular Atrophy*, 84 Neurology 668, 676 (2015), filed as Ex. 70; Ex. 72 (ECF Nos. 72-3; 72-5) ("Scoto")). The child mentioned in Scoto was, Dr. Shuman maintained, about the same age as L.M., and Scoto's authors had identified similar abnormalities in her MRI. *Id.* at 118. The child from Scoto also had similar debilitating symptoms, such as gait deficiencies and related motor issues. *Id.* at 122.[15]

Dr. Shuman defined the structural abnormalities and white matter deficiencies he observed as a preexisting encephalopathy. In his view, alterations in brain structure, if also accompanied by resulting abnormal function (such as head control or motor problems) as well as other evidence of brainstem issues (such as resting loss of muscle tone), could evidence encephalopathy. Tr. at 118, 119, 120, 126–27. He speculated that the abnormal function that L.M. already displays would only continue as she ages. *Id.* at 119. Even though the encephalopathy was only discovered after vaccination, the abnormalities in brain structure and white matter content were enough to constitute an "encephalopathic precondition." *Id.* at 100. However, Dr. Shuman admitted that had a pre-vaccination MRI been performed and revealed nothing, then his conclusions about preexisting encephalopathy would lack foundation. *Id.* at 149.[16]

After an extensive discussion of his conclusions drawn from L.M.'s MRIs, Dr. Shuman turned to the putative role the vaccines L.M. received in February 2011 played in exacerbating her brain abnormalities/white matter deficiency. Dr. Shuman maintained that the vaccines precipitated her seizures (although he did not maintain that the vaccines caused the *preexisting* abnormalities themselves). Tr. at 161. He found the close temporal relationship between the date of vaccination and seizure onset particular significant, characterizing it as "too close to ignore." *Id*. at 133. He deemed her health good prior to vaccination (except for her documented GERD and a URI). *Id.* at 99–100. After vaccination, by contrast, Dr. Shuman described Ms. Sharpe's observations of L.M.—even before she was taken to the Lewistown E.R.—as documented medical evidence of her

[15] On cross-examination, however, Dr. Shuman acknowledged that Scoto's authors had (correctly) identified the same DYNC mutation relevant in this case as the *actual* cause of the observed structural malformations. Tr. at 152.

[16] Although Dr. Shuman's opinion is premised on the determination that L.M. had a preexisting static/structural encephalopathy, he maintained that even if this were not the case, he would still propose that, at a minimum, L.M. had a "genetic propensity" to react to the vaccinations in light of her DYNC mutation, noting that a structural brain malformation was not a prerequisite to injury. Tr. at 169–70, 171.

profound developmental change.[17] *Id.* at 122–24. He specifically identified likely onset as the hours after vaccination, when L.M.'s lack of responsiveness was first evident to Ms. Sharpe. *Id.* at 144.

In support of his statements about the causal relationship between vaccination and L.M.'s symptoms, Dr. Shuman referenced the "National Childhood Encephalopathy Study" performed in the United Kingdom in the late 1970s. *See* Richard Alderslade et al., *The National Childhood Encephalopathy Study: A Report on 1000 Serious Cases of Serious Neurological Disorders in Infants and Young Children from the NCES Research Team*, Reports from the Comm. on Safety of Med. & Joint Comm. on Vaccination & Immunisation (1981), filed as Ex. 36a; Ex. 36b (ECF Nos. 31-8; 31-9) ("UK Study"). In the UK Study, researchers queried whether the pertussis vaccine can cause neurological harm to young children. *Id.* at 141. Based on an examination of the vaccination records of one thousand children between the ages of two and thirty-five months who had been hospitalized with diagnoses such as encephalopathy and West syndrome, the researchers concluded that the "DTP vaccine probably can cause acute neurological reactions." *Id.* at 107, 138, 141.

Dr. Shuman maintained that the UK Study established an association between "serious neurologic illness" and vaccines like DPT.[18] Tr. at 128. In his view, the UK Study, as well as other scientific literature, showed a connection specifically between whole cell pertussis (contained in the DPT vaccine) and incidence of infantile spasms. *Id.* at 369–70 (discussing D.L. Miller, et al., *Pertussis Immunization and Serious Acute Neurological Illness in Children*, 282 British Med. J. 1595 (1981), filed as Ex. 35, ECF No. 31-7 ("Miller"); UK Study).[19] He admitted, however, that the UK Study was dated, especially in light of recent scientific developments and changes to the pertussis component in childhood vaccines (and that there was nothing more recent to which he could point associating vaccines with infantile spasms). *Id.* at 160. Thus, the UK Study did not address the more recent acellular pertussis vaccine forms (which, he acknowledged, had been successfully implemented to reduce the risks observed in the UK Study associated with the whole cell version), although he disputed that introduction of the acellular pertussis component

[17] Dr. Shuman in his testimony attempted to bulwark Ms. Sharpe's assertion that L.M. was in fact feverish not long after vaccination to a greater degree than she reported at the time, noting that because an axillary, or underarm, thermometer was used (which would imprecisely underestimate actual body temperature), L.M.'s temperature was likely even higher than 103 degrees Fahrenheit. Tr. at 125. He later characterized this initial fever as an important piece of evidence linking the vaccinations L.M. experienced to her subsequent seizures and developmental problems. *Id.* at 167–68.

[18] The DPT vaccine covers diphtheria, pertussis, and tetanus. *Liable v. Sec'y of Health & Human Servs.*, No. 98-120V, 2000 WL 1517672, at *1 (Fed. Cl. Spec. Mstr. Sept. 7. 2000). *See* Analysis § I(C), *infra*, for an explanation for the difference between the DPT vaccine and the DTaP vaccine that L.M. received.

[19] On cross-examination, Dr. Shuman admitted that Table VIII in Miller was general in application, referencing "all serious neurologic illnesses" as opposed to infantile spasms specifically. Tr. at 374–75.

completely eliminated all risk. *Id.* at 129–30, 158.[20] He noted further that the package inserts for the vaccines in question also revealed manufacturer awareness of possible adverse effects, the risk of which was multiplied when, as here, several vaccines were administered at the same time. *Id.* at 130.

Dr. Shuman referenced an article filed by Respondent as actually *supporting* his view about the association between infantile spasms and vaccines. Tr. at 370–71 (discussing M. Bellman, et al., *Infantile Spasms and Pertussis Immunisation*, Lancet 1031 (1983), filed as Ex. J, ECF No. 34-2 ("Bellman")). He claimed that Bellman affirmatively established that the risk of developing a spasm disorder is heightened in the days immediately after vaccination. *Id.* at 370–71. Bellman itself does *not* facially seem to support this conclusion, however, because its authors conclude that their data supports the increased incidence of spasms onset in first seven days after vaccination as only applying to *trigger* cases, i.e., those in which vaccines may have triggered an otherwise inevitable neurological event. Bellman at 1033. Bellman thus asserts that pertussis is not a direct cause of infantile spasms for children with normal brains but may precipitate onset in children "in whom [infantile spasms] is already destined to develop." *Id.*

Dr. Shuman nevertheless maintained that Bellman's authors had relied upon a "specious argument" to manufacture the result they wanted, discounting data which was contrary to their desired findings by claiming that the affected individuals had a susceptibility to a seizure disorder. Tr. at 371–72. In effect, he maintained that the reduced incidence of post-vaccination spasms onset on a longer timeframe was misused by Bellman's authors to explain away the significance of a dramatic increase in risk in the *shorter* timeframe. *Id.* at 372–73. When cross-examined about Bellman—and in particular the fact that the conclusions it allegedly reached about vaccine causation of infantile spasms were not corroborated in any *other* subsequent literature filed in the case—Dr. Shuman maintained that such studies were likely wrong (although he did not specify how, and lacks the kind of epidemiologic credentials necessary to make such sweeping assertions). *Id.* at 373, 375–76.[21]

Despite his admitted lack of direct experience in immunologic matters, Dr. Shuman made some effort to provide a more detailed explanation for the mechanism by which he theorized vaccines could interact with the preexisting static encephalopathy he proposed characterized

[20] Dr. Shuman also admitted that the UK Study did not take into account the subsequent discovery of the DYNC mutation's relationship to the kind of injury L.M. had experienced, although he suggested that the study could be updated in light of such discoveries (and implicitly that the outcome of such updating might not be contrary to the original's determinations). Tr. at 160.

[21] Respondent also cross-examined Dr. Shuman as to whether Bellman actually provided a better way of understanding the UK Study's conclusions, revealing that the pertussis vaccine is not a direct causal factor of seizure disorders (as opposed to a precipitating factor of individualized seizures). But Dr. Shuman claimed that the premise of such questioning was wrong. Tr. at 376–77.

L.M.'s condition. As he reasoned, a person like L.M. with structural brain abnormalities and a form of white matter deficiency would be vulnerable to "decompensation" if hit with the immunologic stress of vaccination. Tr. at 131. Thus, L.M.'s preexisting state and dysfunction was primed for further reaction. *Id.* at 132. Dr. Shuman was a bit more specific about the mechanism of causation on cross-examination, maintaining that it was likely a reaction to the pertussis toxin purportedly in the DTaP component of the Pediarix vaccine,[22] which would stimulate her immune system to overproduce cytokines and other immunologic substances. *Id.* at 150.

Besides the above, Dr. Shuman also attempted to offer an explanation for the medical reasonableness of the timeframe in which L.M.'s seizure disorder and subsequent sequelae occurred. He referenced her February 2011 neurologic evaluation as revealing the presence of her disorder, noting that West syndrome could appear suddenly, but that its timing in comparison to the vaccinations she had received (given her preexisting encephalopathy) was not just coincidental. Tr. at 133–34. He admitted that there were some references in the record to L.M. having experienced seizure-like activity before the vaccines were administered, but maintained that there was no prior medical record evidence corroborating that these events had actually occurred (and thus suggesting, without elaboration, that they likely had not). *Id.* at 145–48. He acknowledged, however, that Ms. Sharpe and Mr. Moore might not have understood such prior occasions to constitute seizures. *Id.* at 149.

Dr. Shuman dismissed suggestions by Respondent's counsel that an identifiable alternative cause for L.M.'s symptoms post-vaccination existed. In so doing, he did not contest that L.M. may have suffered from a URI prior to vaccination, but maintained that it could not have constituted enough of a "hit" to trigger the level of reaction that he opined the vaccines had caused. Tr. at 164. For this view, Dr. Shuman relied on Ms. Sharpe's contention that the URI had likely cleared by the time of vaccination—leaving only the vaccines as possibly causal. *Id.* at 165.

Dr. Shuman also briefly addressed the significance of the DYNC mutation as possibly providing a better explanation for the cause of L.M.'s seizures and developmental problems—a concept that did not initially figure into his opinion (because the Ambry Genetics testing results were obtain after his first two reports). He did not dispute that L.M. carries the mutation, as well as the more general point that *some* kind of genetic mutation or irregularity likely explained the structural abnormalities and white matter deficiency that he observed from L.M.'s MRI images. Tr. at 121–22. However (and anticipating Dr. Boles's opinion), he proposed that the precise location of the mutation on the greater gene itself was relevant to the expected "consequences" of the mutation. *Id.* Ultimately, he deferred to Dr. Boles on these matters, given that they were outside of his expertise. His final expert report (filed after the discovery of L.M.'s DYNC mutation)

[22] Pediarix consists of DTaP, hepatitis B, and inactivated polio virus vaccines. See Centers for Disease Control & Prevention, *Pediarix Vaccine: Questions and Answers*, https://www.cdc.gov/vaccines/vpd/hepb/hcp/faqs-hcp-pediarix html.

offered his own analysis of the genetic component to this case, which largely echoed Dr. Boles's emphasis on the importance of location (stem versus stalk) of a DYNC mutation in predicting outcome. Shuman Third Rep. at 6.

On cross-examination, Dr. Shuman acknowledged that his opinion lacked a basis for the conclusion that L.M.'s seizure disorder/developmental problems were worsened by vaccination beyond what would otherwise have been expected given her alleged encephalopathic brain malformation/white matter deficiency. Tr. at 151.

2. *Dr. Richard Boles*

Dr. Boles filed one report in this case and testified at hearing. Ex. 57, dated December 25, 2016, ECF No. 61-1 ("Boles Rep."). His opinion accepts the fact that L.M. had the DYNC mutation and that it played a role in her seizure disorder and related condition, but maintains that the vaccines she received worsened her overall course. Tr. at 183.

As reflected in his curriculum vitae, Dr. Boles received his B.S. from the University of Arizona and his M.D. at the University of California Los Angeles ("UCLA"). Ex. 58 at 2, ECF No. 61-2. He completed a pediatrics residency at Harbor-UCLA Medical Center, followed by a genetics fellowship at Yale University. *Id.* Dr. Boles served as a professor of clinical pediatrics at the University of Southern California from 1993 until 2014. *Id.* at 2. He is board certified in clinical genetics and clinical biochemical genetics. *Id.* at 1. He specializes in clinical genetics and metabolic diseases. Tr. at 172. He has worked for biotech companies but is largely today in private practice, where he "treats people with energy disorder[s]." *Id.* at 225. Dr. Boles's ample expertise in genetics is offset by his admitted lack of expertise in immunology. *See id.* at 207–08, 225.

In his reports and testimony, Dr. Boles discussed at length the nature of L.M.'s DYNC mutation. He agreed she possessed the mutation before the vaccinations at issue, and that it likely was present at her birth. Tr. at 217. He defined it as a "missense" mutation (*id.* at 173), meaning one that causes a gene to code for a different amino acid than normal. *Dorland's* at 1169. He also allowed that the DYNC mutation explained *some* of L.M.'s spasms and other symptoms. Tr. at 179, 193–94 ("I'm concurring with [Ambry's] decision that [the DYNC mutation genetic variant]'s pathogenic"). He nevertheless maintained that certain features of the mutation bulwarked his view that vaccination likely exacerbated L.M.'s condition.

In particular, Dr. Boles opined that the precise location of the DYNC mutation on the DYNC chromosomal protein chain was critical in determining the symptoms an individual would experience when the mutation is expressed. Here, he identified the gene's tail or stem domain—specifically its "dynein complex-binding domain"—as the likely location of L.M.'s mutation, relying on a graphic from one of Petitioner's filed items of literature to illustrate his point. Boles

Rep. at 9; Tr. at 173–74 (discussing A. Strickland, et al., *Mutation Screen Reveals Novel Variants and Expands the Phenotypes Associated with DYNC1H1*, 262 J. Neurology 2124, 2137 (2015), filed as Ex. 82, ECF No. 85-8 ("Strickland")).

Strickland's authors screened over one thousand cases of individuals suffering from motoneuron and related diseases in search in instances in DYNC mutations, locating thirteen patients possessing some form of DYNC mutation. Strickland at 2126. The mutations were distributed across the length of the gene (which Strickland noted to be "one of the largest genes in the human genome") but the pathogenic versions were grouped in the "functional domains" of the gene, suggesting to its authors that "there are regions that are more susceptible to mutation-induced dysfunction." *Id.* at 2131. In particular, Strickland observed (based upon its thirteen-patient sample group) that "intellectual disability mutations are clustered microtubule binding regions"—which Dr. Boles maintained was *not* the location of L.M.'s mutation. *Id.*; Tr. at 173–76.

Dr. Boles acknowledged that the terms "stem" and "tail" were not consistently used in the literature in discussing the location of the DYNC mutation, but that for purposes of his analysis what mattered was that the relevant mutation was *not* found in the section of the gene responsible for motor function. Tr. at 173. A missense mutation found only in the "complex binding domain" of the gene, by contrast, would be less severe than otherwise possible, claiming that he was unaware of any contrary circumstances. *Id.* at 176–77, 181, 365. This was consistent with his report, in which he concluded that an individual with a DYNC mutation located in the motor end of the gene was far more likely to experience a severe outcome than one with a mutation in the stem.[23] Boles Rep. at 10.

As additional support for this proposition, Dr. Boles referenced Scoto, observing that the DYNC mutation for the child in question was located *outside* of the gene domain responsible for motor function. Tr. at 175–76. He also relied upon other items of literature filed, plus case reports. *Id.* at 181–82 (discussing Strickland at 8; S. Gandomi, et al., *Exome Sequencing Identifies Five Mutations in the DYNC1H1 Gene Associated with Severe Neurological Phenotypes* (2014), filed as Ex. 83, ECF No. 85-9 (finding that "mutations in the motor domain and MTBD appear to be associated with more severe neurological phenotypes")). And he claimed that the "vast majority

[23] Dr. Boles in fact attempted to cast this point as statistically significant, maintaining that DYNC mutations located "in the dynein complex-binding domain [are] 23 times more likely to result in either developmental delay and/or epilepsy than is mutation in the *DYNC1H1* gene outside of this domain." Boles Rep. at 10. As a basis for this assertion, he performed his own statistical analysis of the thirteen individual cases discussed in the Strickland plus five more taken from another item of literature. *Id.* Of course, such a small sample size—eighteen cases total—greatly undermines the degree to which it can be characterized as statistically significant. *See* D. Kaye & D. Freedman, *Reference Guide on Statistics, in Reference Manual on Scientific Evidence* 211, 264 (3rd ed. 2011); *see also Jewell v. Sec'y of Health & Human Servs.*, No. 11-138V, 2016 WL 5404165, at *10 (Fed. Cl. Spec. Mstr. Aug. 29, 2016) (expert opining that two studies utilizing sample sizes of 6 and 420, respectively, would need to be much larger to identify a statistically significant risk factor).

of the mutations in the dynein binding or dimerization domain [the area where monomers combine to form polymers][24]" were generally more likely to be severe than tail/stem-located mutations, Tr. at 366–67.

Dr. Boles spent much time in his testimony (particularly during Petitioner's rebuttal case) attacking the argument of Respondent's genetic expert, Dr. Maria Descartes, that a DYNC mutation in the stem/tail region of the gene could also be severe in phenotypic outcome and/or consistent with L.M.'s course. Tr. at 363–67. In particular, he claimed that two articles offered to show that L.M.'s illness course was consistent with others bearing the DYNC mutation involved mutations located "outside the dimerization domain," thus decreasing their relevance to understanding L.M.'s condition. *Id.* at 364 (discussing H. Hoang, et al., *DYNC1H1 Mutations Associated with Neurological Diseases Compromise Processivity of Dyenin-Dynactin-Cargo Adaptor Complexes*, 114 Proceedings of the Nat'l Acad. Of Sci. 1597 (2017), filed as Ex. U, ECF No. 70-2 ("Hoang"); M. Willemsen, et al., *Mutations in DYNC1H1 Cause Severe Intellectual Disability with Neuronal Migration Defects*, 49 J. Med. Genetics 179 (2012), filed as Ex. FF, ECF No. 71-6 ("Willemsen")). He also took issue with accepting the Ambry Genetics prognosis for L.M.'s expected outcome, noting that the test results report did not identify the location of the mutation (and therefore, presumably, missed the importance of that distinction in characterizing expected outcome). *Id.* at 196 (discussing Ex. 42 at 41; Ex. 57 at 8).

Another item of literature offered by Respondent did not involve a missense mutation. Tr. at 365; K. Poirier, et al., *Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A Cause Malformations of Cortical Development and Microcephaly*, 45 Nat'l Genetics (2013), filed as Ex. W, ECF No. 70-4. Only Strickland featured a DYNC mutation in the same location of the gene as that Dr. Boles alleged occurred with L.M., but he maintained that the symptoms of the affected child were more like attention deficit/hyperactivity disorder rather than the "severe intellectual cognitive problem" that L.M. has. Tr. at 365.

L.M.'s receipt of vaccines greatly amplified and worsened the expected, comparatively milder course otherwise attributable to her mutation, Dr. Boles opined. To support this contention, Dr. Boles relied upon both general and specific points. Broadly, he maintained, the field of genetics recognizes that a particular mutation can never be solely responsible for all resulting aspects of a disease it might cause. Tr. at 180. Genetic factors associated with certain outcomes were in his view better thought of as posing risk than "predisposition." *Id.* at 183. Rather, in Dr. Boles's experience, an outside environmental factor was more commonly a primary disease trigger even in the context of genetic factors relevant to the illness. *Id.* at 184. He cited twin studies as corroborative proof of the impact of environment even in the context of shared genetic similarities. *Id.* at 180–81.

[24] *See Dorland's* at 520, 562.

Vaccines could, Dr. Boles reasoned, constitute a sufficient "environmental insult" to exacerbate the effects of an underlying mutation. Tr. at 188, 220. He noted in his report that the entire purpose of vaccines was to "evoke an immunologic response," and therefore there was "no rational reason" to exclude vaccines as possible environmental factors that could spark the pathogenesis of a seizure disorder later resulting in more severe symptoms like developmental regression. Boles Rep. at 11. Indeed, he claimed that "80 percent or more" of instances in which a person like L.M. would experience a seizure disorder would be after an "immunological trigger." Tr. at 210. He did not, however, offer literature specifically addressing the propensity of any vaccine to exacerbate a disease otherwise attributable to a genetic mutation, and this component of his overall opinion had a conclusory character to it, relying more on his *ipse dixit* than independent evidence. *See, e.g.*, Boles Rep. at 11 ("I find it very difficult to believe that the above neurological changes are unrelated to the temporally-associated vaccination. The possibility of this all being due to coincidence exceeds belief").

Dr. Boles also attempted to rebut Respondent's argument that (as evidenced in the Ambry Genetics test results report) another individual who possessed the same DYNC mutation had experienced a course very comparable to L.M., maintaining that there were no more than vague references in literature to this individual that prevented the conclusion that the disease course was similar. Tr. at 182–83. He even denied that there was evidence at all that the two patients' courses were comparable (while admitting that both had infantile spasm disorders accompanied by severe developmental/intellectual difficulties). *Id.* at 200, 367–68. And (somewhat contrary to his overall assertion that mutation location predicted phenotypic outcome) he purported that the genetic testing could not possibly determine the predicted severity of course for someone with the mutation in the first place. *Id.* at 199.

Dr. Boles struggled to offer reliable scientific or medical proof associating vaccines of any kind with the sparking of a seizure disorder connected to the DYNC mutation or some other comparable genetic mutation. Tr. at 204. At best, he referenced familiarity with literature pertaining to instances in which an underlying metabolic disorder was believed to have interacted with vaccines like the measles-mumps-rubella ("MMR") or DTaP,[25] leading to illness/developmental disorders. *Id.* at 203–04, 208. He also proposed that it was reasonable to expect that an individual with the DYNC mutation also likely had energy production dysfunction due to concurrent metabolic problems, although he added that his opinion did not depend upon the finding that L.M. did in fact have an underlying metabolic disorder (and the record contains no such corroborative findings in any event). *Id.* at 222–24. He admitted as well that a number of other possible triggers (such as fasting and over-exercise) could spark a similar pathogenic process

[25] Dr. Boles admitted he could not pinpoint *which* specific vaccine received by L.M. was causal of her illness, but proposed awareness that the MMR and DTaP had been implicated in other contexts. Tr. at 207–09.

in a person susceptible for genetic reasons to a seizure disorder, with a direct wild virus infection the most likely culprit in the majority of cases. *Id.* at 212–13.

As noted, Dr. Boles affirmatively opined that L.M.'s overall course of disease (which he admitted would have involved some seizures and other sequelae attributable to the DYNC mutation) was worse than what she would have experienced absent vaccination. Tr. at 191–92, 201. For support, he referenced his own personal experience treating a set of twins with a predisposing genetic mutation (not the DYNC mutation). *Id.* at 185–86, 202. Both experienced a stomach virus, but the twin with the more acute infection had a more severe course of infantile spasms and resulting developmental difficulties than the other. *Id.* at 185–86. The disparity, in his view, could only be attributable to a different response to an environmental factor. *Id.* at 187. He acknowledged, however, that the Ambry Genetics report and other genetic testing records made no reference to vaccination as having played a role in L.M.'s disease course, although he questioned whether Ambry would have been informed of the vaccinations in the first place. *Id*. at 206.

Dr. Boles also defended the timing of onset of L.M.'s post-vaccine reaction as reasonable. He deemed her "dramatic deterioration" as occurring within three hours of receipt of the vaccines, terming that timeframe "hard to ignore." Tr. at 185. When pressed on cross-examination for the basis for this pronouncement, however, Dr. Boles acknowledged that he relied mainly on the statements of Ms. Sharpe about the deterioration she alleges to have observed in a three-hour window (although he added that he would still deem a timeframe of 12 or even 24 hours to be alarmingly short). *Id*. at 216–17. He also referenced his own personal experience with individuals that he deemed susceptible to a vaccine reaction, stating that it was not uncommon for them to experience a short timeframe after a vaccine trigger. *Id.* at 215.

Finally, Dr. Boles made some effort to harmonize his testimony on causation with that of Dr. Shuman's (which focused on purported preexisting brain structure abnormalities—and significantly was mostly based on reports filed *prior* to the discovery of L.M.'s DYNC mutation). He maintained that his opinion was not dependent on a finding of static/structural encephalopathy, although Dr. Shuman's opinion strengthened his own conclusions, since what he termed brain "migrational defects"[26] could be seen in conjunction with DYNC mutations. Tr. at 219, 221. However, he acknowledged uncertainty as to whether the DYNC mutation would in fact manifest with the brain abnormalities and/or white matter deficiencies pointed to in Dr. Shuman's testimony. *Id.* at 220–21.

[26] Neuronal migration disorders occur when neurons fail to migrate from their locations at birth to their proper neural circuits. National Institute of Neurological Disorders and Stroke, *Neuronal Migration Disorders Information Page*, https://www.ninds nih.gov/disorders/all-disorders/neuronal-migration-disorders-information-page (June 18, 2018); *see also Ellis v. Sec'y of Health & Human Servs.*, No. 13-336V, slip op. at 5 (Fed. Cl. Spec. Mstr. Sept. 6, 2018).

3. *Dr. Maria Descartes*

Dr. Descartes prepared one expert report and testified at hearing for respondent. *See* Descartes Rep. She opined that L.M.'s DYNC mutation was the cause of her seizure disorder and developmental problems. Tr. at 240.

As shown in her curriculum vitae, Dr. Descartes received her A.S., B.S., and M.D. from the University of Puerto Rico. Ex. S at 1, ECF No. 67-2. She completed a residency in pediatrics at San Juan City Hospital in Puerto Rico, followed by a fellowship in genetics at Baylor College of Medicine in Houston, Texas. *Id.* at 2. Dr. Descartes is currently a professor of genetics and pediatrics at the University of Alabama Birmingham ("UAB"). Tr. at 234. She is board certified in generics and pediatrics, among other things. *Id.* at 236. She has treated numerous children and adults with genetic disorders in her career, and also participated in clinical trials for new treatments and drugs. *Id.* at 235, 236. She has also published writings on the topic of medical genetics. *Id.* at 236–37. Dr. Descartes is a participant in UAB's undiagnosed disease program as well, within which she mostly assists in evaluating pediatric patients. *Id.* at 237–38.

Dr. Descartes's testimony began with an explanation of some core genetic concepts. She described genes as "inheritable units" that code the production of different kinds of proteins serving a variety of purposes, from inheritable traits (eye and hair color) to "housekeeping" jobs within the human body. Tr. at 240–42. An individual's "genotype" is their genetic composition, while their "phenotype" embodies the characteristics produced (in part) by that composition. *Id.* at 246. She defined an exon as the coding part of a gene that is transcribed for production of a particular protein. *Id.* at 248. Dr. Descartes took special effort to explain the concept of "conservation" in a genetic context, testifying that a "conserved" genetic sequence is one that has been maintained in evolution from lower species to higher/vertebrate species, thereby signifying its biologic importance. *Id.* at 246–47.

Dr. Descartes also explained what genetic mutations are. Any variation in a genetic sequence can result in a "faulty product," as she put it. Tr. at 243. A missense mutation is one where a particular genetic variance results in the production of an amino acid/protein sequence different from what would otherwise occur. *Id.* at 250. A "de novo" mutation is one that has not been inherited from a parent. *Id.* at 244–45. Such genetic variants occur in part as cells divide and replicate to make new ones, or may be environmentally-triggered, in the process of turning on and off (as certain genes perform their function only at certain times in life, such as during an infant's development). *Id.* at 245–46. The "location" of a particular mutation is simply the place in the protein chain forming the gene where the mutation occurs. *Id.* at 244.

Turning to this case, Dr. Descartes explained that the DYNC mutation impacted the function of a gene intended to code the production of dynein, a protein important to cell function

(particularly aiding in intercellular communication or the movement of internal organelles). Tr. at 247. She characterized the DYNC gene as evolutionarily conserved and therefore critical to biologic development. *Id.* at 258. Dynein, she explained, is important to early brain development, but continues to be relevant thereafter to brain functioning (and thus the genes responsible for its coding do not simply shut down later in life). *Id.* at 248, 275–76. In concordance with the Ambry Genetics test results description, Dr. Descartes noted that the specific mutation in question (one of fifty known variants of DYNC mutations) was located at exon 13, and caused the production of phenylalanine to be replaced by serine. *Id.* at 249, 250.

Dr. Descartes characterized L.M.'s version of the mutation as particularly rare—and, because it was de novo, serious, as de novo mutations are more commonly associated with negative outcomes. Tr. at 252, 280. However, she also acknowledged that it could not be predicted in advance with complete certainty what *any* outcomes would be for individuals bearing DYNC mutations, and that the possession of certain mutations was not necessarily determinative of outcome. *Id.* at 253, 275, 279, 280.

In response to Dr. Boles, Dr. Descartes devoted a large portion of her testimony and expert reports to rebutting Petitioner's proposition that the precise location of the DYNC mutation was significant. She admitted that L.M.'s mutation was located in the gene's stem/tail location. Descartes Rep. at 3. However, although Dr. Descartes acknowledged that mutations in that location were viewed by the relevant literature as *generally* resulting in polyneuropathic symptoms, while mutations found in the gene's stalk/motor domain were associated with more severe intellectual deficits (i.e., cortical malformation, seizure disorders, etc.), she disputed that stem/tail mutations were *invariably* associated only with more benign outcomes. Tr. at 254, 261, 283–84, 289. In her view, a range of outcomes was always possible regardless of mutation location. *Id.* at 266–68. In so proposing, she maintained that it was the mutation *itself* that mattered more than its location, given the overall significance of the DYNC gene's function. *Id.* at 258 ("the gene has all these regions that are very important. They are not static").

To support her opinion, Dr. Descartes referenced several instances in medical literature in which the location of a DYNC mutation was discussed. *See generally* Tr. at 262–66. For example, she mentioned a case report involving one patient with a de novo DYNC mutation in the stem/tail region of the gene who experienced severe intellectual deficits and late onset epilepsy but not the neuropathic symptoms that Dr. Boles had argued were characteristic of tail mutations. *Id.* at 262 (discussing Hoang at 16, Table S1). Hoang (published two years after Strickland) specifically reviewed fourteen individual cases of DYNC mutations in humans, plus three in mice that resulted in motor and sensory defects. In discussing this particular case of a tail-located mutation, Hoang's authors observed that "[r]emarkably, the tail mutation with the strongest effect on processive movements of the dynein-dynactin-BICD2N complex in our study—K129I—*is the one farthest*

away from the motor domain." *Id.* at 9 (emphasis added).[27] Hoang overall is more tentative in embracing the interpretation of Strickland Dr. Boles proposes, emphasizing that overall too much remains unknown about the possible mutations (not all of which are even pathogenic) or the mechanisms effected thereby. *Id.* at 1597, 1603 ("the dynamic changes within the motor complex [resulting from mutation] . . . are only partially understood").

In another piece of literature evaluating the association between the DYNC mutation and polyneuropathies, a patient with a DYNC mutation in the stalk/motor function region experienced only mild intellectual delay (contrary to what Dr. Boles argued would be expected for a mutation in that location of the gene). Tr. at 263 (discussing C. Fiorillo, et al., *Novel Dynein DYNC1H1 Neck and Motor Domain Mutations Link Distal SMA and Abnormal Cortical Development*, 35 Human Mutation 298 (2014), filed as Ex. CC, ECF No. 71-3). Dr. Descartes admitted on cross-examination that DYNC mutations in the stalk/motor function region of the gene would in most cases result in more severe outcomes, but persisted in maintaining that location was overall not a robust predictor. *Id.* at 284.

Turning to the medical records, Dr. Descartes reviewed L.M.'s condition, relating it to the preexisting DYNC mutation. She characterized L.M. as having severe intellectual disabilities, along with evident cortical and brain malformation. Tr. at 259. This outcome was, in Dr. Descartes's view, consistent with her mutation. *Id.* at 254. She could not say if the mutation in this case resulted in a presentation more or less severe than what others similarly situated would face—but cited the existence of *another* person who experienced the DYNC mutation but a similar outcome as evidence that the "pathogenic mutation" was the most likely explanation for L.M.'s symptoms. *Id.* at 259; *see also id.* at 256, 284, and 286.

This individual is only glancingly referenced in the Ambry Genetics report on L.M.'s DYNC mutation. Ex. 42 at 41 (describing L.M.'s mutation as "previously detected internally at Ambry Genetics in a female patient with a history of infantile spasms, intellectual disability, autism spectrum disorder, reduced muscle tone in all extremities, and gray matter heterotopia on MRI"). However, the relevant patient was discussed with somewhat more specificity in a subsequent article. Tr. at 256–57, 268, 270, 288; K. Helbig, et al., *Diagnostic Exome Sequencing Provides a Molecular Diagnosis for a Significant Proportion of Patients with Epilepsy*, 18 Genetics in Med. 898 (2016), filed as Ex. OO, ECF No. 90-1 ("Helbig"). Dr. Descartes testified that she had personally telephoned Ambry Genetics to inquire about the similar patient, whereupon an Ambry Genetics representative informed her that this patient had been reported in the Helbig article. Tr. at 272. That child possessed a DYNC mutation identical to L.M.'s—including location—and a highly similar phenotypic presentation (infantile spasms coupled with a

[27] In discussing the effect of tail mutations, Hoang's authors also noted that "many sites along the [DYNC] tail are involved in regulating motor activity," further diminishing the reliability of the stem/tail versus stalk/motor mutation distinction urged by Dr. Boles. Hoang at 9.

subsequent epileptic encephalopathy). Tr. at 270; Helbig at 11 (Table 3, Patient ID 32).[28] Dr. Descartes admitted that there was no way to determine if the second child had faced the same environmental factors that arguably affected the outcome of L.M.'s mutation (including vaccination). *Id.* at 287. She nevertheless stressed that articles like Helbig recognized the commonalities between the DYNC mutation and the kinds of symptoms L.M. experienced. *Id.* at 269–70.

Dr. Descartes spent some time in her testimony discussing the putative causal role vaccination may have played in L.M.'s subsequent illness. She asserted that she was not aware of literature establishing any connection between the DYNC mutation and vaccination. Tr. at 284–85. She did allow that a wild virus infection could constitute an environmental factor that might interact with the sequelae primarily stemming from a genetic variant, due to a reduced tolerance to infection. *Id.* at 285. But she disclaimed the ability to opine on whether a vaccine could impact the symptomatic course caused otherwise by a mutation absent more specific, reliable studies on the subject. *Id.*

Dr. Descartes more affirmatively denied that L.M.'s outcome was worse than what would have been expected absent vaccination. Tr. at 259. In support, she referenced the Willemsen article, which discusses the overall severe outcomes associated with the DYNC mutation regardless of the mutation's precise location. *Id.* at 259–60. Willemsen evaluated the phenotypic outcome for two patients who possessed a DYNC mutation—one in the stem domain, the other in the motor domain. Willemsen at 181 Fig. 2. Although the phenotypes were not identical, they both featured intellectual disability, and were deemed sufficiently similar to conclude that "de novo mutations in [DYNC] causes variable phenotypes including severe [intellectual disability] with variable neuronal migration defects, and peripheral neuropathy." *Id.* at 179. In citing Willemsen, she also noted that one of the two referenced individuals in that article had experienced brain malformations much like Dr. Shuman observed in the L.M.'s MRIs, along with intellectual deficits and neuropathic symptoms. Tr. at 259–60 (discussing Willemsen at 4). And she cited the patient discussed in Strickland as evidencing the severity of DYNC mutation outcomes and how comparable those outcomes were to L.M.'s experience. Tr. at 260 (discussing Strickland at 6).

[28] Ex. OO was not filed before hearing, nor was it referenced in Dr. Descartes's report, although Dr. Descartes did in her report mention the similar patient when discussing the Ambry Genetics test results report. *See* Descartes Rep. at 3. During cross-examination of Dr. Descartes, Petitioner's counsel pointed these factors out in arguing that the exhibit should not be admitted in evidence. I nevertheless have allowed it in, based upon the general understanding that late-filed evidence, if relevant to the claim, is routinely permitted into the record in the Vaccine Program. Tr. at 272–74. I maintain that holding herein—and note in addition that since the Ambry Genetics testing report unquestionably references the similarly-situated child in the first place, the relevance of the subsequent document (which merely provides more details about the other child) is self-evident, and outweighs whatever slight prejudicial effect its late filing might have. The parties expressly agreed not to file post-trial briefs (tr. at 378), and Petitioner never filed anything after hearing in response to this exhibit.

4. *Dr. John Zempel*

Dr. Zempel, a pediatric neurologist, prepared two reports and was Respondent's second expert witness to testify. *See* Ex. B, ECF No. 21-1 ("Zempel First Rep"); Ex. I, ECF No. 34-1 ("Zempel Second Rep."). He offered the opinion that L.M.'s seizure disorder reflected a "classic presentation" that could not be credibly linked to her vaccinations other than temporally. Tr. at 322.

Dr. Zempel received his B.S. from the University of Wisconsin-Madison, followed by his M.D. and Ph.D. from Washington University in St. Louis. Ex. C at 1, ECF No. 21-2. He completed residencies in pediatrics, adult neurology, and child neurology, as well as fellowships in pediatric epilepsy and clinic neurophysiology. *Id.* at 2. He is board certified in neurology, child neurology, and psychiatry, and was previously also board certified in pediatrics, though he acknowledged that he has not maintained that certification. Tr. at 297. Dr. Zempel divides his professional time between clinical work (inpatient neurology exams involving children with epilepsy and infantile spasm disorders) and teaching at Washington University Medical School, publishing, and acting as a peer reviewer for medical journals. *Id.* at 293–94, 296. He estimates that in his clinical practice he routinely sees between eight and twenty patients per day, and he had examined a patient with infantile spasms disorder within a month of his hearing testimony. *Id.* at 297.

Like Dr. Descartes, Dr. Zempel began by defining certain terms relevant to L.M.'s condition. In his view, the classic term "seizure disorder" was being displaced by the more precise concept of "epileptic encephalopathy," which he defined as including seizures as a symptom attributable to some other, larger "underlying problem in brain function." Tr. at 299 ("[t]he seizures are not the disease"). That brain dysfunction could include other symptoms in addition to seizures, such as developmental regression or delay. Dr. Zempel characterized West syndrome (infantile spasm disorder) as "one of the prime epileptic encephalopathies that involve infants." *Id.* at 298–99.

Dr. Zempel also reviewed his understanding of the term "encephalopathy." He defined it to mean some kind of brain disease, whether short or long-term. Tr. at 298. He rejected the concept of a "structural encephalopathy" proposed by Dr. Shuman, however, positing that the proper way to characterize a brain malformation such as that allegedly present in L.M. was to call it a "structural abnormality." *Id.* at 300. Dr. Zempel differentiated epileptic encephalopathies from an acute encephalopathy, emphasizing that children diagnosed with a spasm disorder that would fall within the category of an epileptic encephalopathy, despite the severity of such a condition, do not suffer from the inability to function normally in many respects that a child suffering from a severe acute encephalopathy would experience. *Id.* at 298, 317.

As Dr. Zempel explained, infantile spasms disorder (named for its classic temporal presentation in infancy) can feature a variety of seizures.[29] Tr. at 300–01. Its clinical definition, however, also requires evidence of hypsarrhythmia corroborated by EEG readings, as well as evidence of developmental delay. *Id.* at 302. It is a progressive condition, and can present first with spasms or be uncovered by EEG absent spasms. *Id.* at 352–53. Because "the syndrome of infantile spasms is more than just the spasms," seizures alone are not, in Dr. Zempel's view, an alarming occurrence capable of leading to "long-term neurodevelopmental problems." *Id.* at 336, 337 ("I don't stress out" when presented with a child experiencing a cluster of overnight seizures, assuming they can be controlled with treatment), 338. Because its initial presentation is not clear-cut in children, it can be difficult for parents to recognize seizure activity as a precursor. *Id.* at 301–02.

Dr. Zempel went on to discuss the possible known causes of infantile spasms, differentiating between symptomatic (where a cause is known) and cryptogenic (spasms similar to the symptomatic kind but where no etiology is understood). Tr. at 304–05. Symptomatic spasms can be caused by brain malformation, stroke or other brain injury (often occurring prenatally), a metabolic disorder, or can have a genetic origin attributable to a chromosomal abnormality such as Down syndrome.[30] *Id.* at 303. EEGs and neuroimaging can aid treaters in identifying if a spasm disorder's source is attributable to brain abnormalities. *Id.* at 304. Advances in genetic testing have also helped establish certain genetic variants as a potential underlying source of a spasm disorder, thereby reducing the number of such disorders deemed cryptogenic. *Id.* at 306–07, 359–60. Dr. Zempel stressed the importance of trying to identify the source of such infantile spasms, given how few causes could be directly treated (meaning that in all other cases the priority of treatment would be limited to controlling the symptoms). *Id.* at 305.

Based upon a review of the medical record, Dr. Zempel agreed that L.M. suffers from West syndrome. Tr. at 309. But he took issue with Dr. Shuman's assertion that L.M. had PNTLE or any other white matter deficiency. He asserted that PNTLE was not a commonly-employed diagnostic term, maintaining that it was subsumed within the category of periventricular leukomalacia ("PVL"), an "all too common complication of extreme prematurity" that was notably severe (especially in comparison to L.M.'s presentation). *Id.* at 310.[31] PVL is often detectable from

[29] In so testifying, Dr. Zempel distinguished between *generalized* seizures, which affect the whole body, and *partial* seizures, which affect only a certain area, such as one limb or the face. Tr. at 300. He also distinguished between different seizures patterns: *clonic* seizures involve jerking movements; *tonic* seizures involve stiffening of the body; and *myoclonic* seizures feature "lightning-quick jerks." *Id.*

[30] Down syndrome results from trisomy of chromosome 21 and presents with moderate to severe developmental disabilities and distinctive facial characteristics. *Dorland's* at 1828.

[31] Importantly, L.M. was born at term (Ex. 1 at 5), yet Dr. Shuman continued to suggest that she suffers from PNTLE or PVL in spite of his concession that these conditions are strongly correlated with prematurity. Tr. at 163.

prenatal screening ultrasounds, and can be confirmed when an at-risk child approaches term by MRI. *Id.* at 311.

Here, however, Dr. Zempel disputed that L.M.'s MRIs supported a PVL, PNTLE, or white matter deficiency diagnosis, noting that his opinion (informed by his own viewing of the relevant MRIs) was echoed by the treating neuroradiologist who performed the MRIs at the relevant time. Tr. at 311; *see generally* Ex. 69. He agreed that L.M.'s ventricles appeared "a little bit generous" in size, but opined that most neuroradiologists would not deem them abnormal, adding that the treaters who actually performed the MRIs at issue did not themselves include "ventriculomegaly" in their recorded findings. *Id.* at 312. He therefore disputed that L.M.'s post-vaccination spasms and sequelae could be attributed to brain abnormality.[32]

Dr. Zempel also questioned Dr. Shuman's assertion that L.M. experienced any *other* form of pre-vaccination encephalopathy. In his view, the only "clinically significant" evidence of an existing encephalopathy would be proof that an infant "doesn't function well." Tr. at 317, 319 ("one good indication of whether someone is severely encephalopathic is whether they can function as a baby or as a human"). But his reading of the record did not support that conclusion. *Id.* at 317. Thus, despite her parents' understandable concerns that L.M. receive the highest quality care, and their valid bases for seeking medical intervention on February 15, 2011, L.M.'s treaters did not deem her initial presentation severe. *Id.* at 319. Dr. Comes, L.M.'s pediatrician, seems to have concurred, and Dr. Zempel also found significant the fact that L.M. did not present in a coma and was otherwise not thought to require immediate transfer to St. Vincent Hospital (despite the views of Mr. Moore and Ms. Sharpe that a transfer was necessary). *Id.* at 318–19. And thereafter, once L.M. received a neurologic evaluation, she was discharged and allowed to go home. *Id.* at 322.[33]

In testifying whether the medical record established that L.M. had experienced an encephalopathy, Dr. Zempel discussed the relevance of fever. He agreed with Dr. Shuman that L.M.'s temperature reading of 103 degrees Fahrenheit (as provided by Ms. Sharpe) was high regardless of the manner in which it was taken, and could reflect a vaccine reaction. Tr. at 320. But Dr. Zempel denied that fever is strongly associated with an existing encephalopathy,[34] and

[32] Dr. Zempel, did, however, acknowledge that the structural issues pointed to by Dr. Shuman could constitute "a sign that [L.M.]'s brain development hasn't been normal," even though he discounted any such developmental problems as causative of her post-vaccination spasms and developmental problems. Tr. at 359.

[33] Because Dr. Zempel did not accept the contention that L.M. had experienced any form of encephalopathy before receiving the vaccinations at issue, he rejected the contention that L.M.'s underlying condition was significantly aggravated by those same vaccines. Tr. at 322.

[34] Dr. Zempel accepted Petitioner's counsel's point on cross-examination that a fever *could* in certain cases be high enough to precipitate brain injury, although he also noted that infants have better tolerance of such high temperatures, and otherwise disputed the concept that L.M. may have merely experienced a "transient" encephalopathy. Tr. at 348–49.

noted that L.M.'s overall presentation at the time she was first taken to the ER did not seem any more severe than when she had been treated for URIs and associated congestion in the early weeks of 2011 prior to vaccination. *Id.* at 319–20. He also admitted on cross-examination that L.M. had displayed a concerning reduced responsiveness at the time of the fever, but disputed that such elements together amounted to evidence of acute encephalopathy meriting hospitalization. *Id.* at 343–44, 350. And he allowed that certain conditions also known to have a genetic cause, like Dravet syndrome,[35] could be provoked by a febrile-caused seizure (which in turn could have a vaccination as the trigger), but argued that not enough is known about such illnesses to say whether vaccination is the primary cause of the condition's progression or simply an event temporally coincidental to an increase in symptoms (especially given that children received certain vaccines at the same age as when Dravet symptoms are known to present and/or expand). *Id.* at 353–56.

Dr. Zempel next attacked Petitioner's theory that vaccination could trigger (or exacerbate) an infantile spasms disorder. He maintained that no persuasive or reliable data associates vaccines with infantile spasms. Tr. at 322–23. Indeed, in his view it would be rare that any external "inciting factor" would cause infantile spasms. *Id.* at 329. Dr. Zempel discounted the evidentiary value of the UK Study given its age, noting that it was performed before imaging or genetic testing of the kind used today to identify etiologies for epileptic encephalopathies was possible, and also that it involved a vaccine component (whole cell pertussis) that has since been mostly abandoned. *Id.* at 323, 325. By contrast, studies like Bellman (performed not long after the UK Study) did *not* find the same association between vaccines and infantile spasms. *Id.* at 325.

In Dr. Zempel's view, Petitioner's case fared no better on the "did cause" side of her claim. Based on his overall reading of the medical records, he termed L.M.'s history to constitute a "classic presentation" of an infantile spasm disorder only temporally coinciding with the vaccines she received in February 2011. Tr. at 322. The course of her illness from before vaccination to the present was in his opinion consistent with "treatment-nonresponsive" individuals suffering from infantile spasms. *Id.* at 334. He agreed that there was no evidence of developmental delay prior to vaccination, and that the records from L.M.'s immediate post-vaccination treatment did suggest some differences in her motor presentation. *Id.* at 340, 342–43. He also acknowledged that some records from L.M.'s time at St. Vincent Hospital revealed reduced responsiveness to parental contact, but noted that those same records revealed that contemporaneous treaters attributed such behaviors to drug reactions (administered in response to her seizure activity) or simple sleepiness. *Id.* at 345–46. He emphasized that reduced responsiveness could not simply be seen as a presenting symptom for developmental decline, given the number of possible factors that could explain it (especially given the context of emergency hospitalization of an infant). *Id.* at 346–47.

[35] Dravet syndrome is a rare seizure condition, also called Severe Myoclonic Epilepsy of Infancy, linked to mutations in the SCN1A gene. *Faoro v. Sec'y of Health & Human Servs.*, 127 Fed. Cl. 61, 63–64 (2016).

Dr. Zempel sought to identify record evidence he felt supported the conclusion that L.M.'s seizure activity likely preceded her receipt of the vaccines at issue. He allowed that L.M.'s GERD symptoms could have resembled spasms, but nevertheless maintained that the records otherwise contained references to incidents suggesting a pre-vaccination onset (although he did not dispute that Ms. Sharpe had properly recognized L.M.'s condition as a reason to bring her to the ER on February 15th). Tr. at 313–14 (discussing Ex. 3 at 15; Ex. 4 at 3), 321, 335–36, 339–40. In fact, he questioned whether the histories provided by Ms. Sharpe and Mr. Moore to treaters of pre-vaccination incidents described GERD symptoms at all. *Id.* at 315–16. He also pointed out items in the medical record that suggested L.M. had poor muscle tone before being vaccinated as well (the kind of symptom Petitioner has argued is evidence of vaccine causality). *Id.* at 340. Dr. Zempel emphasized that as a treater he would generally want to inquire of parents if the seizure activity that prompted them to seek medical intervention predated the reason for their visit, noting that parents often only realize after the most recent (and alarming) seizure event that prior, milder occurrences were related. *Id.* at 314–15, 317 (pointing out how common it is for parents only to recognize that seizure activity has been ongoing after a "larger sentinel event").

Finally, Dr. Zempel directed some of his testimony to the issue of the DYNC mutation and its bearing on the causation question.[36] In his view, the fact that the mutation in question occurred in connection with the DYNC gene—understood to have been conserved through evolution and thus highly important—was strong proof that it was more likely the cause of L.M.'s condition (since an error in an important gene's coding function would be expected to be more calamitous). Tr. at 327. In addition, and as the Ambry Genetics report first revealed, another child like L.M. with the same DYNC mutation experienced a similar outcome, underscoring the mutation's role in causation. *Id.* at 327–28. The temporal relationship between the vaccinations at issue, he added, did not reduce the greater likelihood that L.M.'s condition was mostly attributable to the mutation, stressing that the age-dependent component of infantile spasms meant that their onset would *always* be temporally coincidental to the administration of certain childhood vaccines. *Id.* at 329. And he dismissed the contention that vaccines could significantly aggravate a condition with a genetic source, comparing the DYNC mutation at issue in this case to what is known about Dravet syndrome (caused by a different genetic mutation); the overall course of the latter, he testified, is not affected by vaccination, even if a vaccine can cause a transient symptomatic spike (for example, due to a fever induced by the vaccine). *Id.* at 330–33.

III. Procedural History

As noted above, the case was filed in January 2014, with the petition amended on October 7, 2014, and again on May 27, 2015. *See* Pet.; Am. Pet., ECF No. 15; Second Am. Pet., ECF

[36] Dr. Zempel is not a geneticist, and so I give his comments on this topic less weight than those of Drs. Descartes or Boles. At the same time, however, Dr. Zempel's expertise on the subject of infantile spasms *does* give him a basis for discussing known causes of the condition, including genetic etiologies—and his background in diagnosing and treating the relevant injury far exceeds that of any other expert testifying in this case.

No. 26. In the months following the filing of the petition in this case, Petitioner filed medical records, affidavits, and an expert in support of her claim. Respondent subsequently filed a Rule 4(c) Report on November 14, 2014, arguing that compensation was not appropriate in this case. Respondent also filed an expert report on January 16, 2015, which supported this conclusion. Thereafter, Petitioner filed a supplemental expert report on June 10, 2015, and Respondent submitted a responsive expert report on September 30, 2015. In addition, and as addressed in detail below, Petitioner also filed a "Motion for a Determination of Law Governing Petitioner's Table Significant Aggravation Claim," on February 26, 2016.

The entitlement hearing was held in March 2018. The parties did not elect to file post-trial briefs. Tr. at 378.

IV. Applicable Legal Standards

A. Claimant's Burden in Vaccine Program Cases

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table, corresponding to one of the vaccinations in question and also occurring within a statutorily-prescribed period of time—or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; *see also Shalala v. Whitecotton*, 514 U.S. 268, 270 (1995) (quoting 42 U.S.C. § 11(c)(1)(C)(i)); *Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[37] Petitioner in this case asserts both types of claims.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the

[37] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

When a Table Injury claim is successfully established, causation is presumed. 42 C.F.R. § 100.3. Table claims must satisfy with evidence the specific elements of the relevant claim, including the definitions of terms set in the Qualifications and Aids to Interpretation (the "QAI"). Section 14(b). Case law underscores that, to obtain the benefit of the presumption of causation associated with a Table claim, the claim's requirements must be strictly construed. *Miller v. Sec'y of Health & Human Servs.*, No. 02-235V, 2015 WL 5456093, at *24 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (requiring petitioner to satisfy the "strict Table definition" of encephalopathy).

For a non-Table claim, proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In such circumstances, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner asserting a non-Table claim must satisfy all three of the elements established by the Federal Circuit in *Althen v. Secretary of Health & Human Services*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, the petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v.*

Sec'y of Health & Human Servs., 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017).

In discussing the evidentiary standard applicable to the first *Althen* prong, many decisions of the Court of Federal Claims and Federal Circuit have emphasized that petitioners need only establish a causation theory's biologic plausibility (and thus need not do so with preponderant proof). *Tarsell v. United States*, 133 Fed. Cl. 782, 792–93 (2017) (special master committed legal error by requiring petitioner to establish first Althen prong by preponderance; that standard applied only to second prong and petitioner's overall burden); *Contreras*, 121 Fed. Cl. at 245 ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)); *see also Andreu*, 569 F.3d at 1375. At the same time, there is contrary authority from the Federal Circuit suggesting that the preponderance standard applied when evaluating a claimant's overall success in a Vaccine Act claim also bears on the first *Althen* prong. *See, e.g.*, *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1350 (Fed. Cir. 2010) (affirming special master's determination that expert "had not provided a 'reliable medical or scientific explanation' *sufficient to prove by a preponderance of the evidence a medical theory* linking the [relevant vaccine to relevant injury]") (emphasis added). Regardless, one thing remains: petitioners always have the ultimate burden of establishing their Vaccine Act claim *overall* with preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell*, 133 Fed. Cl. at 793 (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be

accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Standard for Significant Aggravation Claim

In this matter, Petitioner maintains that the relevant vaccines significantly aggravated L.M.'s preexisting genetic mutation or other brain malformation/white matter deficiency. Where a petitioner so alleges, the *Althen* test is expanded, and the petitioner has additional evidentiary burdens to satisfy. *See generally Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (2009). In *Loving*, the Court of Federal Claims combined the *Althen* test with the test from *Whitecotton v. Secretary of Health & Human Services*, 81 F.3d 1099, 1107 (Fed. Cir. 1996), which related to on-Table significant aggravation cases. The resultant "significant aggravation" test has six components, which are:

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

> significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144; *see also W.C.*, 704 F.3d at 1357 (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims"). In effect, the last three prongs of the *Loving* test correspond to the three *Althen* prongs.

Subsumed within the *Loving* analysis is the requirement to evaluate the likely natural course of an injured party's preexisting disease, in order to determine whether the vaccine made the petitioner worse than he would have been but for the vaccination. *Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381–82 (Fed. Cir. 2012) (upholding special master's determination that petitioner had failed to carry her burden of proof in establishing that her preexisting injury was worsened by the relevant vaccine); *Hennessey v. Sec'y of Health & Human Servs.*, No. 01-190V, 2009 WL 1709053, at *41–42 (Fed. Cl. Spec. Mstr. May 29, 2009), *mot. for review denied*, 91 Fed. Cl 126 (2010). The critical point of examination is thus "whether the change for the worse in [petitioner's] clinical presentation was aggravation or a natural progression" of the underlying condition. *Hennessey*, 2009 WL 1709053, at *42.[38] The Federal Circuit has upheld the determinations of special masters that worsening was not demonstrated by a petitioner in connection with establishing her overall preponderant burden of proof for a non-Table causation-in-fact claim. *See, e.g., Snyder/Harris v. Sec'y of Health & Human Servs.*, 553 F. App'x 994, 999-1000 (Fed. Cir. 2014); *Locane*, 685 F.3d at 1381–82.[39]

Application of *Loving's* "worsening" requirement has been the occasion for some disparate holdings by special masters as well as the Court, especially due to the problems posed when evaluating the impact of a preexisting genetic condition that likely played *some* role in an injured party's post-vaccination health. In some cases, the mere fact that an injured party was literally

[38] The legislative history of the Vaccine Act strongly supports interpreting "significant aggravation" as requiring a claimant to establish that a vaccine rendered a preexisting condition qualitatively worse than it would have been otherwise—not simply that the affected individual experienced a post-vaccination symptom that contrasts with the individual's comparatively better pre-vaccination health. *See* H.R. Rep. No. 99-908, at 15 (1986) ("This [significant aggravation] provision does not include compensation for conditions which might legitimately be described as pre-existing (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), *but is meant to encompass serious deterioration* (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis" (emphasis added)).

[39] This is consistent with the fact (well recognized by controlling precedent) that evidence of "worsening" relevant to Respondent's alternative cause burden may reasonably by evaluated by a special master in determining the success of a petitioner's prima facie showing. *Snyder/Harris*, 553 F. App'x at 1000, *quoting Stone*, 676 F.3d at 1380 ("no evidence should be embargoed from the special master's consideration simply because it is also relevant to another inquiry under the statute"); *see also Bazan*, 539 F.3d at 1353 ("[t]he government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief").

"worse" than she was immediately prior to the vaccination at issue has been viewed as sufficient to satisfy this prong. *See, e.g.*, *Paluck v. Sec'y of Health & Human Servs.*, 113 Fed. Cl. 210, 232 (2013), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015).

In other instances, however, the mere fact a vaccine might "trigger" a transient negative response in an individual with an underlying condition has not been deemed proof of worsening if that individual would be expected to experience a similar overall course regardless. *Faoro v. Sec'y of Health &Human Servs.*, No. 10-704V, 2016 WL 675491, at *27 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. for review denied*, 128 Fed. Cl. 61 (Fed. Cl. Apr. 11, 2016) (finding that "the vaccinations would not have changed her clinical course and thus, the vaccinations did not significantly aggravate her preexisting condition"). This point has been emphasized in a subcategory of Program cases involving the claim that a child's Dravet syndrome was significantly aggravated by vaccination. *Faoro*, 2016 WL 675491, at *1. In such cases, special masters have repeatedly determined that petitioners failed to show that a child's expected outcome would have been different but-for the vaccination—even though it was not disputed that the child's first major seizure had been triggered by vaccination. *Id.* at *2 ("[a]lthough H.E.F.'s vaccinations may have caused a low-grade fever or otherwise triggered her first seizure, neither the initial seizure nor her vaccinations caused or significantly aggravated her Dravet syndrome and resulting neurological complications"); *see also Snyder/Harris*, 553 F. App'x 994 (special master was not arbitrary in finding that petitioners' expert failed to show that the child's outcome would have been different had he not received the vaccinations at issue).

In *Barclay v. Secretary of Health & Human Services*, 122 Fed. Cl. 189 (2015), however, the Court of Federal Claims called into question whether *Loving* was the appropriate framework in cases where a genetic basis for an injured party's disease is undisputed. There, Judge Bruggink discussed the fact that "how the genetic abnormality is taken into account" heavily impacted application of the *Loving* factors. *Barclay*, 122 Fed. Cl. at 193. The Court noted that in a case where a child unquestionably possessed a preexisting genetic mutation associated with a particular outcome (in *Barclay*, the SCN1A mutation and its association with Dravet syndrome), the petitioner would logically seek to argue that the vaccine at issue had aggravated the child's pre-vaccination health (which in *Barclay* involved *no* manifestation of seizure activity at all prior to vaccination) by attempting to prove that the vaccine had made the child's future seizures and developmental delay "more severe." *Id.* at 198. The alternative was untenable; the genetic factor was too persuasively associated with seizure activity to rule it out, and the fact that the vaccine (through causing a fever due to its stimulation of the innate immune system) might have directly caused initial seizure activity was "insufficient to establish liability" based simply on the fact that the child thereafter recovered (if briefly) from it. *Id.*

As a result, *Barclay* suggested that the *Loving* analysis might actually not be an "ideal fit" for cases involving a genetic mutation. Instead, a better way to approach such a case would simply

be to evaluate Respondent's success in carrying his counter-burden of establishing that a "factor unrelated" to the vaccine was the cause of injury. *Barclay*, 122 Fed. Cl. at 193 (*citing Knudsen*, 35 F.3d at 547). Doing so would avoid requiring a petitioner to establish a disease prognosis in light of the preexisting genetic mutation (which *Barclay* deemed to constitute a heightening of the Petitioner's underlying burden of proof). *Barclay*, 122 Fed. Cl. at 198–99.

C. Law Governing Factual Determinations

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such a determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"); *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs*., 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms. It is equally unlikely that pediatric neurologists, who are trained in taking medical histories concerning the onset of neurologically significant symptoms, would consistently but erroneously report the onset of seizures a week after they in fact occurred").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs.*, No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir.), *cert. denied sub nom. Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y Health & Human Servs*., 110 Fed. Cl. 184, 203–04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records over contrary testimony, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

D. Analysis of Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc*., 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339).

E. Consideration of Medical Literature

Both parties relied on medical and scientific literature in this case in support of their respective positions. I have reviewed all of the medical literature submitted in this case, although my decision does not discuss each filed article in detail. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted).

ANALYSIS

I. Overview of Law Pertaining to Specific Injuries Alleged

A. Infantile Spasms

Petitioners seeking an entitlement award on the basis of the claim that a vaccine precipitated a child's seizure disorder have succeeded. Many of these cases involve the DTaP vaccine or its predecessor, the DPT vaccine (the differences between which are discussed below), as well as the pneumococcal vaccine. *E.g.*, *Graves v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 310 (2011) (reversing special master's denial of entitlement; pneumococcal vaccine caused seizure activity resulting in child's death even in absence of fever); *Kottenstette v. Sec'y of Health & Human Servs.*, No. 15-1016, 2017 WL 6601878 (Fed. Cl. Spec. Mstr. Dec. 12, 2017) (vaccines (including DTaP and pneumococcal) caused infantile spasms disorder); *but see Arango v. Sec'y of Health & Human Servs.*, No. 09-318V, 2012 WL 4018028 (Fed. Cl. Spec. Mstr. Aug. 23, 2012) (DTaP and pneumococcal vaccines, among others, not causal of infantile spasms disorder, rejecting both Table and non-Table claims), *mot. for review denied*, 109 Fed. Cl. 335 (2013). L.M. received both such vaccines in February 2011, before the ER visit alleged to have been the first instance in which she experienced a seizure.

There is no real dispute in this case as to the elements of West syndrome/infantile spasms. As explained by Dr. Zempel and reflected in the filed medical literature, West syndrome is a form of seizure disorder experienced by infants and characterized by seizures (the spasms) *plus* hypsarrhythmia and subsequent developmental problems. A. Arzimanoglou, et al., *Epilepsy in Children: Ch. 3—Infantile Spasms and Related Syndromes* 1–32 (3rd Ed. 2004), filed as Ex. F, ECF No. 21-5 ("Arzimanglou"); Tr. at 300–02, 352–53. Spasms are "often associated with developmental arrest or regression," and "[m]any infants become severely disabled, physically and intellectually, even when no underlying cause is found." A. Lux, et al., *The United Infantile Spasms Study (UKISS) Comparing Vigabatrin with Prednisolone or Tetracosactide at 14 Days; A Multicentre, Randomised Trial*, 364 Lancet 1773, 1773 (2004), filed as Ex. 30, ECF No. 31-2. On average, onset of spasms occurs at five months of age. *Id.* at 1775. While the etiology of West

syndrome is often unknown, known causes include enzyme deficiencies, perinatal maternal drug abuse, meningitis, and cerebral palsy. Andrew L. Lux et al., *The United Kingdom Infantile Spasms Study (UKISS) Comparing Vigabatrin with Prednisolone or Tetracosactide at 14 Days; A Multicentre, Randomised Trial*, 4 Lancet Neurology 712, 716 (2005), filed as Ex. 31, ECF No. 31-3.[40]

However, cases in which a child is found to have possessed a preexisting genetic mutation known to be associated with phenotypes involving seizure disorders are a different matter entirely. The weight of such authority goes against the conclusion that *any* vaccine could significantly aggravate the expected course of disease—even where it was *not* disputed that the vaccine might nevertheless be responsible for triggering an initial seizure. *See generally Oliver v. Sec'y of Health & Human Servs.*, No. 10-394V, 2017 WL 747846 (Fed. Cl. Spec. Mstr. Feb. 1, 2017) (vaccines, including DTaP and pneumococcal, did not significantly aggravate underlying mutation associated with seizure disorder, although fever attributable to vaccination was trigger for initial seizures), *mot. for review denied*, 133 Fed. Cl. 341 (2017), *aff'd*, 900 F.3d 1357 (Aug. 17, 2018); *Faoro*, 2016 WL 675491 (vaccines including pneumococcal and DTaP did not significantly aggravate child's SCN1A mutation resulting in seizures and developmental delay); *Barclay v. Sec'y of Health & Human Servs.*, No. 07-605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014) (DTaP vaccine did not significantly aggravate Dravet syndrome otherwise attributable to SCN1A mutation), *mot. for review denied*, 122 Fed. Cl. 189; *Taylor v. Sec'y of Health & Human Servs.,* No. 05-1133V, 2012 WL 4829293 (Fed. Cl. Spec. Mstr. Sept. 20, 2012) (same), *mot. for review denied*, 108 Fed. Cl. 807 (2013); *Snyder v. Sec'y of Health & Human Servs.,* No. 07-59V, 2011 WL 3022544 (Fed. Cl. Spec. Mstr. May 27, 2011), *mot. for review granted,* 102 Fed. Cl. 305 (2011), *rev'd*, 553 Fed. App'x 994 (Fed. Cir. 2014) (same).[41]

The overlap between such cases and the present action is striking. All involve circumstances in which a child's preexisting genetic mutation was acknowledged by the petitioner,

[40] Exhibits 30 and 31 discuss the same scientific study, but provide different analytical angles. Both provided distinct and useful background information on West syndrome/infantile spasms.

[41] Even though it established the framework for a significant aggravation claim, *Loving* is an outlier in finding that the DTaP vaccine *did* significantly aggravate a child's infantile spasms predating vaccination. There, however (and unlike the present case), it was not established that the child in question had any genetic mutation specifically associated with a phenotypic presentation consistent with the child's disease course. The child's spasm disorder also already existed at the time of vaccination, allowing the Court to focus on the pure question of whether vaccination altered the expected course of his disorder. *Loving*, 86 Fed. Cl. at 137. In this context, the Court found significant the fact that the DTaP vaccine was specifically contraindicated for individuals already diagnosed with a seizure disorder. *Id.* at 138. Otherwise, the case turned on the timing in which the exacerbation occurred, as well as the extent to which conclusions could be drawn about a systemic response to vaccination from a record that did not contain evidence of the child's post-vaccination reaction. *Id.* at 148–52. Here, by contrast, the record is well-developed with respect to (at least) L.M.'s post-vaccination health, and timing is less of a dispositive issue given the predominance of questions raised about her preexisting DYNC mutation, which is understood to be associated with her specific presentation.

but nevertheless alleged to have been affected by vaccination—whether because the vaccine triggered a fever which produced a seizure and thereby "unmasked" the genetic variant, or more generally because vaccination was an environmental factor that interacted with the child's immune system sufficient to complicate his otherwise expected outcome. *See generally Oliver*, 2017 WL 747846, at *1 n.3 (collecting fifteen Vaccine Program decisions rejecting the theory that a seizure disorder was triggered in a child with a preexisting genetic mutation). However, it is also the case that almost all of these parallel cases involve a specific genetic mutation (the SCN1A mutation) known to be associated with a phenotype consistent with what the injured child experienced, *and* that reliable medical research had demonstrated that this mutation produced the same outcome regardless of whether a child experienced a "triggering" seizure that unmasked its pathologic character. There is no dispute herein that L.M's mutation is not an SCN1A variant (although its similar expected phenotypic outcome means that SCN1A cases have some bearing on this case's resolution).

B. Encephalopathy

The kind of facts supportive of a finding that an injured party experienced an encephalopathy depend on whether the petitioner advances a Table or non-Table claim. As discussed in more detail below, the requirements of establishing a Table encephalopathy are precise and quite rigorous. The Table's definition of the term "simply does not encompass every type of brain dysfunction to which the broader meaning of 'encephalopathy' applies." *Wright v. Sec'y of Health & Human Servs*., No. 12–423V, 2015 WL 6665600, at *6 (Fed. Cl. Spec. Mstr. Sept. 21, 2015); *Fester v. Sec'y of Health & Human Servs*., No. 10–243V, 2013 WL 5367670, at *21, n. 5 (Fed. Cl. Spec. Mstr. Aug. 27, 2013). By contrast, a claim involving a non-Table encephalopathy can be based on more expansive understanding of the term. As noted by former Chief Special Master Vowell, the term encephalopathy, "as commonly used in the medical community, encompasses a much broader class of injuries than the more stringent definition of acute encephalopathy found in the QAI [qualifications and aids to interpretation]." *Wright*, 2015 WL 6665600, at *5 (citing *Waddell v. Sec'y of Health & Human Servs*., No. 10-316V, 2012 WL 4829291, at *6 (Fed. Cl. Spec. Mstr. Sept. 19, 2012)).

C. Injury-Causing Capacity of Pertussis, DPT, and DTaP Vaccines

In finding that a child's spasms were caused by vaccination, a few cases in the Vaccine Program involving a pertussis-containing vaccine elide differences in the formulation of such vaccines, assuming that their pathogenic capabilities are indistinguishable for purposes of determining entitlement. *See, e.g.*, *Kottenstette*, 2017 WL 6601878, at *13–14 (because the injured child's spasms would have qualified her for inclusion in studies involving the DPT vaccine, the findings of those studies (which associated the DTP vaccine with spasms) applied to her even though she received the DTaP vaccine). However, there *is* a significant distinction between the

DPT vaccine and the subsequent forms that use the acellular version of pertussis—and it bears directly on the propensity of the version of pertussis vaccine most commonly administered today to promote seizures.

The Pediarix combined vaccine that L.M. received in 2011 included DTaP, a component of which is intended to immunize against infection by the *Bordetella pertussis* bacterium that causes whooping cough, "an acute contagious infection of the upper respiratory tract, seen in young children." *Dorland's* at 1421. The version of the pertussis vaccine that was previously widely administered was a "whole cell" vaccine, meaning a "suspension[] of the entire *B. pertussis* organism that has been inactivated." *Pertussis*, World Health Organization (May 21, 2015).[42] The acellular version, by contrast—which L.M. received—is formulated from antigens isolated from the *Bordetella pertussis* bacterium (including inactivated pertussis toxin as well as other protein components of the bacterium) and then purified or detoxified. *See Grace v. Sec'y of Health & Human Servs.*, No. 04-[redacted], 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006). It was developed specifically to address certain adverse reactions that had been observed in connection with the whole cell version's administration.

In a decision from approximately twelve years ago, former Special Master Hastings took the above into account in noting that "[t]he DTaP version, in general, is believed by medical scientists to be much improved, and to be much less likely than the DPT vaccine to cause neurologic reactions or other harmful side effects." *Grace*, 2006 WL 3499511, at *9. As a result, the expert in that case improperly relied on findings pertinent to DPT in attempting to establish that a child's infantile spasms were attributable to DTaP vaccine (a claim that Special Master Hastings rejected, albeit not solely for this reason). *Id.* at *13–14.

Subsequent decisions have underscored that the DTaP vaccine's injury-causing potential cannot be conflated with findings pertinent only to the DPT whole-cell version.[43] *See, e.g.*, *Taylor v. Sec'y of Health & Human Servs.,* No. 05-1133V, 2012 WL 4829293, at *30 (Fed. Cl. Spec. Mstr. Sept. 20, 2012) ("[i]t is well established that, while pertussis toxin may be capable of causing neurological damage, vaccination, especially modern-day vaccination with *the acellular form,* is generally safe") (emphasis added). Special masters have therefore been critical of expert attempts to apply medical or scientific research pertaining to the DPT vaccine to the TDaP form. *Holmes v.*

[42] https://www.who.int/biologicals/vaccines/pertussis/en.

[43] Importantly, it is *not even* the case that medical science has established an association between infantile spasms and the older, whole-cell pertussis vaccine. *See Taylor*, 2012 WL 4829293, at *1 ("decades of epidemiological research into the issues presented in this case—whether pertussis vaccination causes West Syndrome—has not yielded reliable evidence of a causal link"). As a result, there is a lengthy set of special masters decisions stretching back over 25 years that do not find petitioners succeeded in connecting infantile spasms to the pertussis vaccine. *See generally Grace*, 2006 WL 3499511, at *12 (citations omitted). While those decisions do not control the outcome of this case or even reflect evidence before me, their holdings involved an evidentiary weighing process similar to that I am called upon to perform herein (and even similar evidence), and I thus take some limited note of them.

Sec'y of Health & Human Servs., No. 08-185V, 2011 WL 2600612, at *20 (Fed. Cl. Spec. Mstr. Apr. 26, 2011) (noting that expert in question had previously attempted to extrapolate conclusions from studies involving DPT to TDaP vaccines), *citing Simon v. Sec'y of Health & Human Servs.*, No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1, 2007) ("the relative risks of an adverse event from a DPT vaccine found in those DPT related epidemiologic studies do not attach to a DTaP vaccine"). Such decisions have also specifically noted that certain literature or studies that Petitioner's experts herein rely on, like the UK Study, are not reliable scientific evidence supporting causation. *See, e.g., Taylor,* 2012 WL 4829293, at *28 (UK Study only revealed a "temporal shift" in which an increased incidence of reported cases of infantile spasms was observed closer in time to vaccination than later, but that this increase could be attributed merely to parental vigilance or an underlying causal genetic factor); *Simon*, 2007 WL 1772062, at *7.

II. Petitioner's Table Claim

A. Petitioner's Proposed Table Claim Interpretation is Legally Untenable

Ms. Sharpe's Table claim alleges that L.M. "suffered a significant aggravation of a pre-existing encephalopathy," with the first manifestation of that aggravation occurring within three days of L.M.'s receipt of the DTaP vaccine[44] on February 10, 2011. Pet. Brief at 15. Applying the relevant terms as they are set forth in the Table, to prevail on her Table significant aggravation claim Ms. Sharpe must demonstrate that: (a) L.M. experienced an "encephalopathy" prior to receipt of the DTaP vaccine on February 10, 2011; (b) L.M. suffered a significant aggravation of that encephalopathy after vaccination; and (c) the first symptom or manifestation of the significant aggravation of L.M.'s encephalopathy occurred within seventy-two hours after her February 10, 2011 DTaP vaccination. Sections 11(c)(1)(C)(i), 14(a), 33(4); 42 C.F.R. § 100.3(a) (2017).

Before addressing if Petitioner can meet this definition, there is a preliminary matter to resolve: what is the proper Table definition for "encephalopathy" in the context of a claim alleging significant aggravation? *See generally* "Motion for a Determination of Law Governing Petitioner's Table Significant Aggravation Claim," dated February 26, 2016, ECF No. 40 ("Table Mot."), and accompanying memorandum of law, ECF No. 41 ("Memo."). Petitioner raised this issue well before hearing, but I ultimately deferred its resolution, since the proof that would be offered for Petitioner's non-Table claim would be the same. I am now prepared to rule on this pending question of law.

[44] Of the vaccines administered to L.M. in February 2011, only the DTaP vaccine can be the basis for a Table claim alleging significant aggravation of a preexisting encephalopathy.

The Table defines encephalopathy in the following manner:

(2) *Encephalopathy*. A vaccine recipient shall be considered to have suffered an encephalopathy if an injury meeting the description below of an acute encephalopathy occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.

(i) *Acute encephalopathy*.

(A) For children less than 18 months of age who present:

(1) Without a seizure, an acute encephalopathy is indicated by a significantly decreased level of consciousness that lasts at least 24 hours.

(2) Following a seizure, an acute encephalopathy is demonstrated by a significantly decreased level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state—from a seizure or a medication.

42 C.F.R. §§ 100.3(c)(2)(i)(A)(1–2) (2017).

*** * ***

(C) The following clinical features in themselves do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, poor feeding, persistent inconsolable crying, bulging fontanelle, or symptoms of dementia.

(D) Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy and in the absence of other evidence of an acute encephalopathy seizures shall not be viewed as the first symptom or manifestation of an acute encephalopathy.

42 C.F.R. §§ 100.3(c)(2)(i)(C–D) (2017).

* * *

(1) *Chronic Encephalopathy*.

(i) A chronic encephalopathy occurs when a change in mental or neurologic status, first manifested during the applicable Table time period as an acute encephalopathy or encephalitis, persists for at least 6 months from the first symptom or

manifestation of onset or of significant aggravation of an acute encephalopathy or encephalitis.

42 C.F.R. § 100.3(d)(1)(i) (2017).

* * *

(4) Significantly decreased level of consciousness is indicated by the presence of one or more of the following clinical signs:

(i) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);
(ii) Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
(iii) Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

42 C.F.R. §§ 100.4(d)(4)(i–iii) (2017).

Petitioner, however, argues that the "common, ordinary, and accepted meaning" of "encephalopathy" should be used when deciding her Table significant aggravation claim, rather than the above definition, "because the language of 42 CFR 100.3(b)(2) limits its [QAI] application to onset cases." Table Mot. at 2 (citing *Waddell v. Sec'y of Health and Human Services*, No. 10-315V, 2012 WL 4829291, at *8 (Fed. Cl. Spec. Mstr. Sept. 19, 2012) (special master should use the ordinary meaning of 'encephalopathy' because the statute and regulations do not provide a definition)). In her view, the black-and-white QAI definition is nonsensical, because under it "[n]o petitioner can demonstrate that her *pre-vaccination* illness, injury or condition 'manifests' 'within the applicable period' *after vaccination* specified in the Vaccine Injury table." Memo. at 2.

In support of this argument, Petitioner relies on a decision written by former Chief Special Master Golkiewicz, *DeRoche v. Sec'y of Health & Human Servs.*, No. 97-643V, 2002 WL 603097 (Fed. Cl. Spec, Mstr. Mar. 28, 2002). In it, the special master found that it was "infeasible" to apply the existing Table definition of "encephalopathy" to a Table significant aggravation claim, because the language in the definition dealing with post-vaccination onset rendered devoid a claim based on aggravation of a *preexisting* encephalopathy. *Id.* at *27. Thus, although a Table encephalopathy claim based on receipt of the DTaP vaccine required proof that the encephalopathy had acutely manifested within seventy-two hours of vaccination, the very fact that the claim was one for significant aggravation presupposed that the encephalopathy already existed.

However, although *DeRoche* proposed a reading of "encephalopathy" that (as discussed below) simply excised the portions incompatible with a significant aggravation claim while

retaining the majority of the remaining parts of the definition (*DeRoche*, 2002 WL 603097, at *29), Petitioner asks me to totally disregard its proposed reading (despite the embrace of *DeRoche*'s reasoning in subsequent decisions like *Wiechart v. Secretary of Health & Human Services*, No. 07-283V, 2007 WL 4285328, at *3 (Fed. Cl. Spec. Mstr. Nov. 21, 2007) (utilizing revised definition of encephalopathy first enunciated in *DeRoche*)). Memo. at 8. That reading, in Petitioner's estimation, still relies on an understanding of encephalopathy that pertains only to cases in which identifying onset is the critical issue. I should instead utilize the "common, ordinary, and accepted" meaning of "encephalopathy" when determining whether L.M. suffered a pre-vaccination encephalopathy, referencing *Waddell* to support her contention that undefined terms in the Table should be given their ordinarily-understood meaning. Memo. at 6 (citing *Waddell*, 2012 WL 4829291, at *9; *Nuttall v. Sec'y of Health & Human Servs.*, No. 07-810, 2015 WL 691272, at *10 (Fed. Cl. Spec. Mstr. Jan. 20, 2015)).

Respondent disputes Petitioner's arguments about the proper construction of a significant aggravation Table claim involving a pre-vaccination encephalopathy. *See* Respondent's Response to Petitioner's Motion for a Determination of Law Governing Petitioner's Table Significant Aggravation Claim, April 25, 2016, ECF No. 44 ("Opp."). In so arguing, Respondent mostly maintains that the evidence in this case does not establish an "acute" encephalopathy, relying on the QAI definition over Petitioner's objection. Opp. at 7–9. Respondent otherwise maintains that neither *DeRoche* nor *Wiechart* are binding and thus should not determine the definition of encephalopathy in this matter. *Id.* at 9–10 n. 7.[45]

Because Petitioner's argument centers on *DeRoche*, it is worth examining that decision more carefully. There, former Chief Special Master Golkiewicz expressly recognized the extent to which the Table definition of encephalopathy was in tension with a Table significant aggravation claim based on an alleged pre-vaccination encephalopathy. *DeRoche*, 2002 WL 603087, at *29 ("[t]he literal application of [Section] 100.3(b)(2) to presumptive significant aggravation claims, as required by [Section] 11(c)(1)(C)(i), leads to absurd results and thwarts [C]ongressional intent to provide petitioners a Table significant aggravation theory of recovery and a corresponding definition for encephalopathy-based cases"). But in so ruling, he did not jettison completely the Table definition, as Petitioner contends. Instead, the special master removed the phrases "within the applicable period" and "and then a chronic encephalopathy persists in such persons for more than 6 months beyond the date of vaccination" from 42 CFR § 100.3(b)(2), relying on what

[45] Petitioner filed a reply that refined somewhat the argument she originally made with respect to the proper definition of encephalopathy within a Table significant aggravation claim. Reply, May 13, 2016, ECF No. 47. She now maintains that I should merely determine if L.M.'s post-vaccination status was evidence of worsening of her alleged pre-vaccination encephalopathy, and not require that this evidence *itself* establish encephalopathy as defined by the QAIs. *Id.* at 2, 4–6. Because, as noted in *Whitecotton*, special masters are free to consider evidence from outside the table time period in determining whether an individual suffered the first symptom or manifestation of a significant aggravation of an injury within the table time period, I should "consider all the available evidence and keep in mind that symptoms first documented on February 15, 2011 may have begun on February 10, 2011." *Id.* at 6.

remained of the Table definition (including the QAIs pertaining to "acute" encephalopathy) to decide the petitioner's claim. *Id.* at *27. This modified reading was subsequently embraced by a different special master. *Wiechart*, 2007 WL 4285328, at *3.

Petitioner's argument—which simultaneously asks me to follow *and* reject *DeRoche*—is unpersuasive. *DeRoche* reasonably interpreted the definition of encephalopathy so as to permit Table claims for significant aggravation of a preexisting encephalopathy by judiciously limiting what it excised from the definition (in particular, language requiring proof of a preexisting chronic encephalopathy). But it does not constitute a total abandonment of the Table definition, as Petitioner urges. *DeRoche* is consistent with the federally-recognized guidelines of statutory construction that favor narrow excisions of inconsistent language over wholesale rejection of an entire provision. *See Green v. Bock Laundry Machine Co.*, 490 U.S. 504, 511–27 (1989) (finding that, as written, Federal Rule of Evidence 609(a)(1) "can't mean what it says," but choosing to read the rule narrowly rather than throw out the rule altogether); *see also Mountain States Tel. & Tel. co. v. Pueblo of Santa Ana*, 472 U.S. 237 (1985) (narrowly modifying the reading of a statute "so as not to render one part inoperative") (citations omitted); *Hellebrand v. Sec'y of Health & Human Servs.*, 999 F.2d 1565, 1570–71 (Fed. Cir. 1993).

Successful Table claims require petitioners to make a precise factual showing, meeting definitions that are often more narrow than what a claimant would have to establish for a non-Table claim (as observed above in comparing the Table and non-Table treatment of "encephalopathy"). *DeRoche* reasonably accounted for the contradiction in the Table definition of encephalopathy by excising only the portion of the definition that negated a significant aggravation claim. It did *not* hold that the Table definition was *entirely* void for this reason, and its logic for so determining is consistent with the federal common law approaches to statutory construction.

Based on the foregoing, I find that to establish a Table claim of significant aggravation of an alleged preexisting encephalopathy, Petitioner must meet *DeRoche's* harmonized definition of "encephalopathy," relying on most of how that is defined in the Table, and therefore proving at a minimum that L.M. experienced a pre-vaccination "acute" encephalopathy as set forth in the QAIs.

B. Petitioner Has Not Demonstrated that L.M. Experienced a Pre-Vaccination Acute Encephalopathy as Defined by the Table

Applying the above, the facts in this case do not support the conclusion that L.M.'s brain structural irregularities, or pre-vaccination symptoms, rose to the level of an "acute encephalopathy." The Table definition of acute encephalopathy does not encompass the kind of structural brain malformation observed by Dr. Shuman. Dr. Shuman's diagnosis of PNTLE was also not persuasive, as it lacked sufficient scientific foundation (and appears largely to rely on white matter deficiency conditions like PVL most commonly associated with prematurity—something that does not characterize L.M.'s birth). His assessment that L.M. had a preexisting

brain malformation was otherwise rebutted by analysis of L.M.'s treating physicians—in particular, the radiologists who reviewed the same initial MRIs but deemed them largely normal. And although it is not disputed by either party that L.M.'s DYNC mutation *preceded* vaccination, an underlying genetic disorder does not, by itself, constitute encephalopathy given the term's definition in the QAIs.

The record also does not provide support for the conclusion that L.M. experienced a "decreased level of consciousness" prior to receiving the DTaP vaccine. And there is nothing about her pre-vaccination status, as reflected in the medical records or the statements of Petitioner and Mr. Moore, that smacks of an acute condition significant enough to warrant hospitalization. At best (although it is not a fact accepted by Petitioner), in the month before vaccination, L.M. experienced some initial seizure activity likely related to her post-vaccination infantile spasm disorder—but the Table explicitly *excludes* seizure as sufficient evidence for a finding of acute encephalopathy. 42 C.F.R. § 100.3(b)(2)(i)(3)(D). Thus, because the evidence in this case does not meet the QAI definition of encephalopathy, Petitioner's Table claim cannot succeed.

III. Petitioner's Causation-in-Fact Significant Aggravation Claim Fails

Ms. Sharpe's non-Table claim focuses on both L.M.'s DYNC mutation and "subtle cortical malformations" alleged to exist by Dr. Shuman, maintaining that the vaccines she received (not limited to the DTaP) in February 2011 constituted an "epileptogenic stimulus" sufficient to produce "profound neurologic injury" given L.M.'s preexisting conditions (which placed her at an increased risk of injury). Pet. Brief at 27–28. Below, I address the *Loving* factors in order of their significance to my decision, rather than in their ordinal sequence.

A. *Loving* Prong Three: the Petitioner did not Successfully Establish that L.M.'s Post-Vaccination Condition was Sufficiently Worse to Constitute a "Significant Aggravation" of her DYNC Mutation

The lynchpin of a non-Table significant aggravation claim is the demonstration of "significant aggravation." As noted above, it is not enough for a claimant to establish that (in contrast to his pre-existing health) he was "worse" after the vaccine in comparison to his health immediately before, and that this initial worsening is plausibly attributable to the vaccine negatively interacting with a preexisting condition. Rather, the claimant must demonstrate that his or her post-vaccination condition is overall *qualitatively* worse than what would be expected given what is known about the preexisting condition (which might otherwise have deleterious effects on its own). *Locane*, 685 F.3d at 1381–82; *Hennessey*, 2009 WL 1709053, at *42.

Petitioner was unsuccessful in meeting this *Loving* prong. There is no question that she possesses the DYNC mutation,[46] and both experts agreed that the mutation is associated with poor outcomes overall consistent with L.M.'s course (although, as discussed below, Dr. Boles unsuccessfully attempted to establish that the location of L.M.'s mutation predicted a less severe outcome). Moreover, the medical record does not allow the conclusion that L.M.'s trajectory was appreciably worse after receiving vaccines in February 2011. At best, the record establishes that L.M. experienced some infantile spasms after vaccination (and likely had *already* experienced some even if her parents did not recognize them as such), and then over time experienced more severe developmental problems, consistent (as Dr. Zempel persuasively testified) with what a child possessing a genetic variant known to be associated with such an outcome would experience. Beyond the manifestation of L.M.'s West syndrome itself, the record does not support the conclusion of a dramatic worsening (for example, the February and April MRIs are largely consistent) post-vaccination.

Certainly Petitioner made several sound arguments regarding L.M.'s course consistent with her overall claim. The record does supports the conclusion that L.M.'s condition was worse *immediately* post-vaccination (if compared only to her immediate pre-vaccination condition). In addition, Petitioner has pointed to evidence from the medical record that L.M. displayed some motor control issues and diminished responsiveness on February 15, 2011, after the seizure that resulted in her being taken to the hospital—although such evidence must be balanced against the fact that by the time of her discharge from St. Vincent Hospital two days later, she had returned to baseline (and indeed the fact that she *was* discharged cuts against the conclusion that she had dramatically worsened on the 15th, as treaters were comfortable letting her go home).

But to argue that this meets the legal standard of significant aggravation is to misapprehend that standard, at least as applied in cases involving genetic variants like the DYNC mutation *known* to be associated with outcomes largely consistent with what L.M. experienced. *See, e.g.*, *Faoro*, 2016 WL 675491, at *25. That legal standard requires an evaluation of what is known about the preexisting mutation and its likely impact on an affected individual's life. Here, preponderant evidence (while not as conclusive as that pertaining to the SCN1A mutation) still favors the determination that L.M.'s outcome would most likely be as it was regardless of vaccination.[47]

[46] Petitioner also maintained (via Dr. Shuman's testimony) that L.M.'s brain structural malformation could have been aggravated, but the underlying assumption for that position—that she *did* possess such a malformation (and/or white matter abnormality)—was not persuasively established on this record by Dr. Shuman, as discussed below. Accordingly, I primarily consider the genetic variant that L.M. definitively possesses—and, as both Drs. Boles and Descartes agreed, unquestionably was pathogenic in some respect in this case.

[47] As discussed above, the court in *Barclay* noted that genetic mutation cases might be better analyzed under the "factor unrelated" analysis rather than requiring such petitioners to satisfy the *Loving* significant aggravation standards by proposing an expected prognosis. *Barclay*, 122 Fed. Cl. at 193 (citing *Knudsen*, 35 F.3d at 547). Although in this case I do not find that Petitioner carried her initial burden, even if I had I would find that Respondent *did* establish a "factor unrelated," in the form of the relationship between the DYNC mutation and L.M.'s illness. Once a petitioner makes a prima facie showing of causation, "the burden shifts to respondent to demonstrate by a preponderance of the

L.M.'s overall course is consistent with what is known about the effects of a DYNC mutation. The evidence therefore does not preponderate in favor of the conclusion that L.M.'s spasm disorder otherwise attributable to her DYNC mutation was worsened by vaccination.

B. *Loving* Prong Four: Petitioner's Causation Theory was Unreliable

Loving prong four, which echoes *Althen* prong one, requires a petitioner to put forth a plausible and scientifically reliable theory of causation. The Petitioner in this case has failed to do so.

Dr. Shuman's opinion was overall the weaker of the two, especially in light of the fact that his first two reports were filed *prior* to the determination that L.M. possessed the DYNC mutation, and thus proposed a theory that did not take into account a significant fact. Even at hearing, however, Dr. Shuman did not abandon his initial theory. His proposal that L.M. had a pathogenic brain malformation was not corroborated by the medical record (and specifically by the MRIs upon which that opinion relied). His assertion that she alternatively had some kind of white matter deficiency relied upon a diagnosis that not only L.M. never received but which elevated a diagnostic concept (PNTLE) into something that it does not appear medical science recognizes with any degree of trustworthy sufficiency. And his arguments about the capacity of pertussis toxin-containing vaccines to promote seizure activity relied heavily on somewhat outdated medical literature like the UK Study and/or involved conflation of the DPT vaccine with the DTaP version L.M. actually received.

This leaves only Dr. Boles's opinion, which forthrightly acknowledged the existence of L.M.'s DYNC mutation and its pathogenic character, but argued that the precise location of the mutation on the gene predicted an otherwise more favorable prognosis that was made worse by vaccination. This theory certainly raised interesting and valid scientific points regarding the significance of the mutation's location, and was based on the undisputed fact that L.M.'s mutation was located in the stem/tail gene location rather than the more critical motor function location. It

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evidence that a 'factor unrelated' to the vaccine 'was the sole substantial factor in bringing about the injury.'" *Hammitt v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 719, 726 (2011), *aff'd* sub nom. *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373 (Fed. Cir. 2012) (citing *Bazan*, 539 F.3d at 1352). In this case, preponderant evidence was offered by Respondent not only that the DYNC mutation is *generally* associated with outcomes similar to what L.M. experienced, but also that an individual with the same mutation and location as L.M. experienced a parallel course. Tr. at 270; Helbig at 11. I also give some weight to evidence offered relating to the SCN1A mutation. Unquestionably this mutation is not identical to the DYNC mutation, and there is far more robust proof (especially in the form of studies considering the impact of vaccination on such affected individuals) that the SCN1A variant's course is only transiently impacted by the immunologic stress of a vaccination. Nevertheless, the science and literature regarding this mutation (as reflected in the numerous decisions—repeatedly upheld on appeal—denying causation) is persuasive support for the conclusion that genetic mutations understood to have poor phenotypic presentations consistent with an injury alleged to be vaccine-caused are a more reliable explanation for that presentation than the vaccine. And Dr. Descartes's testimony on this point was more reliable than Dr. Boles's, who admitted that the mutation itself is generally pathogenic, but who did not persuasively establish that location was determinative of likely outcome.

also was based in part on reliable scientific literature discussing the significance of mutation location. *See, e.g.*, Strickland at 8. Nevertheless, the theory was flawed in two critical respects.

First, Dr. Boles did not establish with reliable proof Petitioner's contention that location was *as* outcome-determinative as he maintained in his testimony. At most, he offered literature supporting the conclusion that all things being equal, a stem or tail mutation would be less severe in comparison located in the motor/stalk location. He did not provide support for the contention that *any* DYNC mutation did not have some capacity to produce a severe phenotype—or one consistent with what L.M. experienced—despite being located in the stem/tail region.

Consideration of two ostensibly dueling pieces of literature in this case—Strickland and Hoang—demonstrates the insufficiencies in Petitioner's argument. Based on a very small sample size, Strickland does observe some differences in the phenotypic outcomes for DYNC mutations based on where the mutation occurs on the gene, and its conclusions are scientifically reliable as far as they go (although, as noted by Respondent, Strickland *did* observe at least one individual who experienced significant intellectual disability for a mutation in the stem/tail region). However, Hoang, published two years after Strickland, simultaneously expands upon scientific knowledge of the nature of DYNC mutations and calls into question the idea that mutation location is strongly outcome-determinative. Indeed, Hoang *specifically observes* another instance of a tail mutation with an outcome congruent with the kind Petitioner argues are only found when the mutation occurs in the motor region. Hoang at 8–9, Table S1.

Besides Hoang, Respondent offered other compelling evidence demonstrating that the location of a genetic mutation is not alone predictive of mutation outcome. Tr. at 268–70 (Dr. Descartes describing the individual in the Helbig article index with DYNC mutation in stem/tail also suffered from infantile spasms and epileptic encephalopathy). Such literature acknowledges the comparative difference in location and outcome, but concludes that it is the mutation *itself* that is pathogenic overall (and not that a more benign location will inherently mean a more favorable outcome).

Scoto, for example, provides a gene structure map identifying the location on the DYNC gene of the position of different mutations either studied specifically in the article or previously reported in other literature. Scoto at 673 fig. 1. As it indicates, "the mutations identified in this study to cause both [spinal muscular atrophy with lower extremity predominance] and [malformations of cortical development][48] *can be seen to span the entire length of the protein*," and thus phenotypes associated with more severe cognitive impairment could also be seen derived from mutations not solely in the motor domain. *Id.*; *see also id.* at 677 ("[o]ur findings confirm

[48] Dr. Boles's report acknowledged that "spinal muscular atrophy with lower extremity predominance," or SMA-LED, is the kind of phenotypic outcome more commonly observed in association with tail-located mutations and is not deemed as severe. Boles Rep. at 9–10.

that heterozygous missense [DYNC] mutations can lead to a wide range of neuronal migration defects in association with a variable degree of cognitive/behavioral impairment"). Other literature reaches the same conclusion. *See, e.g.*, Willemsen at 4 (comparing two individuals—one with a DYNC mutation in the stem domain, the other in the motor region—but finding that both displayed severe intellectual disability, and (even allowing for the difference in outcome as possibly relating to mutation location) concluding that "de novo missense mutations in [DYNC] are a novel cause of severe [intellectual disability] associated with variable neuronal migration defects").

More persuasively, there is the Ambry Genetics report, which similarly acknowledges differences comparatively in mutation location and outcome, but does not bulwark the importance of location for purposes of predicting likely outcome. In fact, the report's allusion to a child with a DYNC mutation having a phenotype qualitatively comparable to what L.M. experienced was particularly telling in revealing the deficiency of Dr. Boles's argument. Consistent with the Ambry Genetics report, Dr. Descartes's report noted that the relevant variant involved an alteration in a specific amino acid (p.F1093S) located in the stem domain of the gene. Descartes Rep. at 3; Ex. 42 at 41. Helbig, which provides somewhat more detail about the comparable patient alluded to in the Ambry Genetics report, confirmed that this same individual possessed the *precise* same amino acid alteration location as L.M., and an outcome comparable to that experienced by L.M.. Helbig at 11. While such evidence does not rebut Dr. Boles's overall point that location of the mutation affects phenotype, it *does* rebut his point that location *alone* suggests a "more likely than not" phenotypic outcome.[49]

All in all, Petitioner's argument advanced about the significance of mutation location as bearing on severity of outcome had some reliable scientific support. But it did not go far enough to establish a fully reliable theory—not only because not enough is yet known about the interplay between mutation location and outcome for DYNC mutations to conclude as Petitioner urges, but (more compellingly) because the similarly-situated patient identified in Helbig and the Ambry Genetics test results report experienced almost the *same* outcome as L.M.—belying Petitioner's argument about the conclusions that can be drawn about DYNC mutation location. No doubt future research may better demonstrate the significance of location and its determination of phenotype, and may in a different Vaccine Program case make it easier to conclude that a tail-located DYNC mutation is unlikely to be pathogenic in the manner relevant herein. But such research does not yet exist, and on the present record I do not find that Petitioner's showing established the first "can cause" *Althen* prong.

[49] The fact that the female patient referenced in Helbig and the Ambry Genetics test results report might *not* have received any vaccines—a point raised by Dr. Boles in his argument that the environmental factors affecting the unnamed individual were unknown, thus reducing the comparability of her circumstances—actually only strengthens the relevance of this data point. For if the unnamed patient experienced the *same* outcome as L.M. without vaccination, the conclusion that the vaccines had no impact on L.M.'s outcome is strengthened.

Dr. Boles could not invoke or rely upon his own individual experience to counter the above. His demonstrated expertise on genetic matters was not paired with comparable experience studying the DYNC mutation, the genetic sources of West syndrome, or the consistent treatment of such patients over his career, rendering his opinion on mutation location significance with respect to phenotypic outcome less compelling. I thus cannot conclude on such a showing that a stem/tail DYNC mutation would inherently *not* present as it did in L.M.'s case.

The second deficiency in Petitioner's theory is more fatal to the claim. Even if I were to assume for sake of argument that Petitioner's tail-located DYNC mutation meant a less severe outcome than she in fact experienced, Dr. Boles did not persuasively explain *how* the vaccines interacted with the mutation to worsen than anticipated phenotype—or even that they *could* do so. He is not an immunologist, could not refer to specific expertise in studying the impact of vaccination on mutations, and offered no literature speaking to the connection between vaccination and genetic outcome (where a specific mutation is known to have a negative phenotypic presentation) that could fill such experiential gaps. Instead, Dr. Boles relied on personal supposition, or the general proposition that vaccination constitutes an environmental factor that can interact with genetic expression, basing such contentions on his own generalized observations from the treatment of unspecified twins. *See, e.g.*, Tr. at 185; Boles Rep. at 11. Such argument was effectively rebutted by Respondent's comparison of the DYNC mutation to the extensive literature regarding the SCN1A mutation, and the fact that in the latter case the environmental impact of vaccination was *not* deemed significant enough to alter the course otherwise plotted by the preexisting mutation.[50]

Absent support in Dr. Boles's testimony for the connection between vaccines and a mutation-driven pathologic disease, Petitioner was left with Dr. Shuman's points about the seizure-inducing potential of the DPT vaccine - which is not interchangeable with the acellular version administered in this case. She also did not offer persuasive reliable evidence establishing that the pneumococcal vaccine could negatively interact with *any* mutation let alone the DYNC variant. At most, such evidence establishes that a vaccine might (especially if causing fever) spark a *transient* seizure—not that it would worsen a spasm disorder otherwise understood to be genetic in origin.

C. *Loving* Prong Five: the Vaccines at Issue did not Worsen L.M.'s Seizure Disorder

Upon review of the record as a whole, I cannot conclude that it is more likely than not that the vaccines L.M. received on February 10, 2011, "did cause" a worsening of the course of her seizure disorder.

[50] Petitioner perhaps could have rebutted evidence offered about SCN1A mutations by showing that the phenotype for this mutation is (as argued with the DYNC mutation) *also* gene location-dependent, but no such argument or evidence was offered.

The record *does* support the conclusion that L.M. experienced a post-vaccination fever and some reaction the evening of February 10, 2011, after she received the vaccinations at issue. But it is more difficult to determine the degree to which this reaction persisted over the next several days. Although Ms. Sharpe was credible in explaining her observations of L.M.'s state between February 10th and 15th, contemporaneous records from L.M.'s initial presentation at the Lewistown ER suggest that any vaccine-related fever or reaction had subsided by the time of the seizure that led Ms. Sharpe to seek medical intervention (thus underscoring that the initial vaccine reaction was likely transient). Ex. 3 at 13. L.M.'s overall presentation subsequently—both at Lewistown as well as St. Vincent hospital thereafter—reveals evidence of the obvious manifestation of the seizure disorder but does not suggest an acute worsening that could be vaccine-related. Accordingly, the record best supports the conclusion that L.M. had some reaction to vaccination, and that this reaction was closely followed by seizure activity—*not* that the overall seizure disorder was made worse by vaccination.

The record discussed above also reveals the likelihood that L.M. had *already experienced* seizures before the February 15th ER visit. Ex. 3 at 13 (reporting "unexplained episode of sudden flaccidity and unresponsiveness for 30 sec" a month prior). Such pre-vaccination seizure activity was similarly reported at St. Vincent later that same day. Ex. 4 at 3. This evidence is also consistent with Dr. Zempel's testimony (confirmed in filed medical literature) that parents often do not recognize initial seizure activity as part of a greater disorder before a more alarming seizure incident. Tr. at 301–02; Arzimanoglou at 3 ("the spasms often go unnoticed"). Thus, if L.M.'s seizure activity (like her underlying genetic DYNC mutation) predated vaccination, it becomes more difficult to conclude that the February 10th vaccinations worsened it.

The testimony of Petitioner's experts could not rebut the above. Both admitted that they found particularly compelling the fact that L.M.'s West syndrome became most obvious after vaccination – in other words, that the latter preceded the former. Tr. at 133, 185. But it is axiomatic in the Vaccine Program that a mere temporal relationship between vaccination and illness does not establish causation. *McCarren v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 142, 147 (1997).

This leaves L.M.'s DYNC mutation as the most compelling explanation for her predisposition to develop a seizure disorder. At most, the vaccines she received in February 2011 (due to the fever they caused) may have resulted in a transient seizure four days later. However, it is quite likely that L.M.'s seizures in fact began prior to vaccination, and the evidence does not support the contention that her vaccinations thereafter precipitated a substantial worsening of her expected course given her underlying genetic mutation. There is nothing else in this record that suggests that post-vaccination, L.M. experienced an immunologic reaction sufficient to appreciably aggravate her genetic propensity to develop a seizure disorder.

D. Other *Loving* Prongs

Turning to *Loving* Prongs One and Two, it cannot be disputed that L.M.'s underlying DYNC mutation predated the vaccination, but that (although she more likely than not exhibited some symptoms pre-vaccination), she was in better health before February 10th. In addition, her symptoms were undoubtedly more severe and pronounced post-vaccination, and therefore she was literally "worse" thereafter—although as discussed above, L.M.'s deterioration does not ultimately correspond with *Loving* prong three's worsening requirement.

I do find that the onset of L.M.'s seizures after vaccination occurred in a medically-acceptable timeframe (*Loving* prong six) based upon Petitioner's theory. The record establishes that she experienced a seizure within four days of receipt of vaccines on February 11, 2011. This timeframe is medically reasonable under Petitioner's causation theory, and is also consistent with other cases that have found seizures to be vaccine-caused. *See, e.g.*, *Simon*, 2007 WL 1772062. Because, however, I have not also found that the theory that vaccines in question *could* worsen the expected outcome of a DYNC mutation-associated seizure disorder was plausible and/or reliable, and because the record does not support the conclusion that the vaccines were more likely than not the cause of L.M.'s overall condition (even if I allow that the vaccines triggered the February 15th seizure), the fact that the timing is acceptable does not result in a different overall outcome.

CONCLUSION

The record does not support Petitioner's contention that the vaccines L.M. received could, or did, injure her as alleged. Nor did she establish a fundamental aspect of *any* significant aggravation claim: that L.M.'s overall state, given her preexisting DYNC mutation, was rendered worse by the vaccines she received. And her Table claim was rooted in a legally untenable reading of the claim. Thus, although I have tremendous respect for the loving struggles of Ms. Moore and Mr. Hanson to care for their daughter (and also to identify an explanation for her developmental problems), I am required to evaluate their claim on the basis of its success in meeting the legal evidentiary burdens set by the Vaccine Act and controlling Federal Circuit precedent, rather than on sympathies they deservedly elicit.

Petitioners have not established entitlement to a damages award, and therefore I must DISMISS their claim. In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accordance with this decision.

IT IS SO ORDERED.

/s/ Brian H. Corcoran

Brian H. Corcoran
Special Master