In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

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MICHAEL MAGER, as parent of VICTORIA MAGER,	*	
	*	No. 14-820V
	*	Special Master Christian J. Moran
Petitioner,	*	
	*	
v.	*	Filed: April 19, 2022
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Remand; entitlement; human papillomavirus ("HPV") vaccine; epilepsy; significant aggravation; challenge-rechallenge; timing; death
	*	
Respondent.	*	
* *		

Renee J. Gentry and Julie Kim, Vaccine Injury Clinic, George Washington University Law School, Washington, DC, for petitioner;
Zoe Wade and Tyler King, United States Dep't of Justice, Washington, DC, for respondent.

RULING FINDING ENTITLEMENT TO COMPENSATION[1]

Michael Mager alleged that the human papillomavirus ("HPV") vaccine his deceased daughter Victoria received on September 11, 2012, significantly aggravated an epilepsy. He sought compensation pursuant to the National Childhood Vaccine Injury Compensation Program.

After a previous decision found that Victoria did not suffer from a particular form of epilepsy, autoimmune epilepsy, the Court of Federal Claims held that this

[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this ruling on its website. This posting will make the ruling available to anyone with the internet. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

focus on autoimmune epilepsy was erroneous. The Court, accordingly, vacated the previous decision and remanded for an analysis of whether the 2012 vaccination harmed Victoria.

On remand, the parties presented testimony from three people. Mr. Mager called Yuval Shafrir, M.D., a neurologist. The Secretary called Michael H. Kohrman, M.D., a neurologist, and Robert S. Fujinami, Ph.D., a specialist in immunology, although not a medical doctor. Based upon this testimony as well as the written material, the undersigned finds that Mr. Mager is entitled to compensation.[2]

I. Facts

Victoria's history can be separated into three periods. These are (A) from birth to the first dose of the HPV vaccine at age 12, (B) from the first dose of the HPV vaccine to the second dose of the HPV vaccine approximately five years later, (C) from the second dose of the HPV vaccine to Victoria's death.

A. Events and Health Before the First Dose of the HPV Vaccine on October 2, 2007

Victoria Mager was born on July 29, 1995. Amend. Pet., filed Nov. 19, 2014, at ¶ 1. Victoria had a family history of epilepsy on her mother's side. Three cousins on her maternal line had seizures similar to the seizures that Victoria eventually experienced. Exhibit 11 at 28, 40; exhibit 6 at 2. In addition, Victoria's maternal grandfather had epilepsy for which he was treated with surgery. Id. The testifying neurologists recognize that Victoria had a family history of seizures. Tr. 218, 221 (Dr. Shafrir), 447-48 (Dr. Kohrman). In other words, she had a genetic propensity to develop seizures. Id. at 221, 332 (both Dr. Shafrir). For Dr. Kohrman, the family history contributes to Victoria's relatively early onset of juvenile myoclonic epilepsy ("JME"). Id. at 454, 502.

An early medical record from her four-year well-child exam indicates that Victoria's parents had been divorced for about six months. Exhibit 18 at 19. In this November 2, 1999 well-child exam, Victoria's mother informed the pediatrician, Dr. Jason Wray-Raabolle, that Victoria "does not speak much, and others will occ[asionally] have a hard time understanding her." Id. Dr. Wray-Raabolle offered Victoria an evaluation by a speech therapist, but Victoria's

[2] The undersigned has considered all the material in the record, although this ruling does not discuss all the material. This ruling focuses upon the evidence that the parties have emphasized.

mother stated that "she feel[s] her daughter is improving and does not wish to [pursue] that at this time." Id. at 21.

This concern about speech recurs about one year later as part of the five-year well-child exam. By this time, Victoria had started kindergarten. Victoria's mother stated others had difficulty understanding Victoria's speech. Id. at 12 (Sept. 6, 2000).

In another well-child exam about 18 months later, Victoria's mother reported that Victoria was receiving speech therapy. Exhibit 18 at 3 (Mar. 11, 2004). Victoria was in second grade, and she was earning Ds in some subjects. Id. According to a neuropsychologist's report created in 2008, Victoria had an individualized education plan ("IEP") from first to fourth grade, and an IEP in speech and language from grades four through seven. Exhibit 6 at 1; accord Tr. 280 (Dr. Shafrir), 510 (Dr. Kohrman). However, any IEP is not among the exhibits. Dr. Kohrman saw Victoria's learning difficulties as consistent with JME. Tr. 455; see also id. at 539.

In the March 11, 2004 appointment, Victoria's mother informed the pediatrician that Victoria was wetting the bed. Exhibit 18 at 3. At this time, Victoria was eight years old. A non-contemporaneous medical record indicates that the bedwetting started when Victoria was around six years old. Exhibit 6 at 25 (Dr. Koehn's Feb. 21, 2008 report). It appears that Victoria was placed on Ditropan.[3] In addition to the bedwetting, Victoria's pediatrician noted that she was receiving speech therapy and experienced "poor performance" and "decreased attention" at school. Exhibit 18 at 5.

Victoria was weaned off Ditropan in summer 2007, about three years after bedwetting was first reported. See exhibit 6 at 25; exhibit 11 at 30. The records indicate that Ditropan helped with Victoria's bedwetting. Exhibit 6 at 25. After stopping Ditropan, Victoria had a few episodes of bedwetting between summer and November 2007. Id. One report states that the bedwetting "stopped . . . completely" after Victoria began to use Depakote, an anti-seizure medication, in November 2007. Id. When asked about these records at hearing, Dr. Kohrman stated that the medical records indicate her bedwetting improved with Ditropan before she received the first HPV vaccine but did not stop completely. Tr. 515. He reasoned that the reference in the records that states the

[3] Ditropan prevents bedwetting by relaxing the bladder, allowing it to expand to contain more urine. Tr. 334. Ditropan is not an antiepileptic medication. Id. at 242.

bedwetting stopped after starting Depakote implies that Victoria was wetting the bed, at least to some degree, until she started taking Depakote. Id. Dr. Kohrman further reasoned that the cessation of bedwetting after taking an anti-seizure medication indicates that the bedwetting was due to seizures. Id. at 446, 511-12, 541.

On this point, Dr. Kohrman was persuasive. Episodes of bedwetting in a child from age seven-years to approximately twelve-years is unusual. See Tr. 242, 329 (both Dr. Shafrir's testimony that approximately 10% of children are wetting the bed at age six and of this group, half stop by age seven).[4] Episodes of bedwetting can be the only manifestation of nocturnal seizures. Exhibit H (Margaret N. Shouse & Mark W. Mahowald, Epilepsy, Sleep, and Sleep Disorders, in Principles and Practice of Sleep Medicine 863 (Meir H. Kryger et al. eds., 4th ed. 2005)) at 870; see also Tr. 328 (Dr. Shafrir: bedwetting could be consistent with a seizure), 501-02 (Dr. Kohrman: bedwetting that continues until age 13 and is stopped after the introduction of anti-seizure medication indicates a nocturnal seizure).

Based in part upon this information, Dr. Kohrman opined that Victoria's neurologic problems started before the first HPV vaccination. Exhibit A at 11-12. The basis is threefold. First, Victoria had problems in school. Second, Victoria was wetting the bed. Third, Victoria was biting her tongue. The first two points were described above. Id.; see also Tr. 445-46; Spec. Mstr. Oral Arg. Tr. 618, citing Tr. 543 (Dr. Kohrman's testimony).

With respect to tongue biting, the evidence is mixed, but favors a finding that Victoria was biting her tongue before vaccination. Some evidence supports this finding. On November 15, 2007, a neurologist, Dr. Uzma Sharif, obtained a history in which she recorded, "Parents have noted tongue [difficult to read]." Exhibit 11 at 40.[5] Later, when seeing the family in follow-up, Dr. Sharif recommended that Victoria's stepmother (Kathy Mager) keep a journal, documenting any episodes of bedwetting, tongue biting, soreness, and wet pillow

[4] Mr. Mager takes a statement from Dr. Kohrman about the commonness of bedwetting in young children out of context. Pet'r's Posthear'g Br., filed Mar. 25, 2022, at 21, quoting Tr. 501-02.

[5] During the hearing, the undersigned asked Dr. Kohrman whether he could read the last word and Dr. Kohrman stated he could not. Tr. 515. On redirect, the Secretary's attorney leadingly asked whether the word could be "lacerations." Id. at 543. Mr. Mager's attorney objected, and this objection was sustained. Id.

with saliva. Id. at 77. The November 15, 2007 history from Dr. Sharif is consistent with a history obtained one day earlier in which a doctor recorded: "Episodes waking up [with] cuts in mouth." Id. at 28.

Thus, the evidence is clear and convincing that before Victoria's generalized tonic-clonic seizure on November 14, 2007, she was biting her tongue. Even Dr. Shafrir agreed on this point. He wrote: "everybody agreed that she probably had episodes of nocturnal seizures during the previous month." Exhibit 55 at 17; accord Tr. 254, 262 (Dr. Shafrir's testimony that Victoria "quite likely" had nocturnal seizures before November 14, 2007). Mr. Mager also agrees that Victoria bit her tongue before the generalized tonic-clonic seizure on November 14, 2007. See Pet'r's Posthear'g Br., filed Mar. 25, 2022, at 20-21; Spec. Mstr. Oral Arg. Tr. 627-28. The ensuing question is whether the tongue biting also started before the October 2, 2007 vaccination.

Two pieces of evidence support a finding that Victoria began biting her tongue before the first vaccination. First, when Victoria went to the hospital on November 14, 2007, in the context of explaining no history of seizures, her stepmother informed the doctor that Victoria had

> 2 questionable episode[s] of
>
> 2 month[s] ago
>
> 2 week[s] ago

Exhibit 11 at 30.[6] An episode that occurred two months before November 14, 2007 would be approximately September 14, 2007, meaning before the vaccination.

Second, when the family sought care from a neurologist (Dr. Koehn) in February 2008 (approximately three months after the tonic-clonic seizure), Mr. Mager told this doctor "that months before this incident happened, Victoria did complain that a couple of times she bit her tongue when she woke up in the morning." Exhibit 6 at 25; accord Tr. 445. Again, "months" before the November 14, 2007 tonic-clonic seizure places the onset of tongue biting before the vaccination. See Tr. 266.

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[6] The doctor's note regarding "month" is not clear. The number before "month" could be a "1" or a "2." See Tr. 266 (Dr. Shafrir, interpreting this note as a "1"); id. at 541 (Dr. Kohrman, interpreting this note as a "2").

Mr. Mager attempted to refute the accuracy of these records. Relying upon Shapiro v. Secretary of Health & Human Services, 101 Fed. Cl. 532, 539 n.10 (2011), mot. for reconsideration denied after intervening remand, 105 Fed. Cl. 353 (2012), Mr. Mager argued a contemporaneous record cannot refer to events taking place months earlier. Spec. Mstr. Oral Arg. Tr. 605-07; see also Pet'r's Posthear'g Br. at 20-21. The upshot to Mr. Mager's argument appears to be that because doctors first documented tongue biting months after the tongue biting reportedly occurred, the tongue biting did not occur when the reports said it did.

The evidence that the tongue biting started after the vaccination was created much later in time, and, therefore, is less reliable. In 2013, a neurologist (Dr. Edgar) obtained a history that began with Victoria experiencing her first tonic-clonic seizure in 2006. It continues: "One month prior to the seizure event, she awoke and had bitten her tongue. A few weeks prior to this, she had received an HPV shot." Exhibit 9 at 6. Dr. Shafrir relies upon this record, despite its creation approximately five years after the events in question. Tr. 241-42, 255; cf. id. at 542 (Dr. Kohrman: a person's memory is altered by events). While this record provides some evidence that the HPV vaccination preceded any tongue biting, this record carries less weight because it was created many *years* later. Although Mr. Mager may be correct that Dr. Koehn's February 21, 2008 record is not contemporaneous with events happening in July 2007, Mr. Mager has not persuasively justified why Dr. Edgar's record from 2013 is more likely to be accurate. Moreover, an additional reason for not crediting the history Dr. Edgar obtained in 2013 is that the history is erroneous in describing Victoria's first seizure as occurring in 2006, when the first tonic-clonic seizure was actually in 2007. Exhibit 9 at 6. Given these inaccuracies in recollections presented in 2013 about events occurring in 2007, crediting Mr. Mager's affidavit from July 15, 2015 (exhibit 19 at ¶¶ 4-6) is also not possible. See O'Connell v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 891, 893, 895 (1998) (denying motion for review when a special master declined to credit the parents' oral testimony because the passage of time may have tainted their memories), aff'd in unpublished op., 217 F.3d 857, 1999 WL 1039699 (Fed. Cir. 1999).

For these reasons, a preponderance of evidence supports placing the tongue biting before the vaccination. Furthermore, there is no meaningful dispute that tongue biting can be a symptom of a seizure. Tr. 265, 328 (both Dr. Shafrir).

Consequently, preponderant evidence supports a finding that Victoria was experiencing seizures before the vaccination.[7] This finding can be made despite

[7] Mr. Mager argued against a finding that Victoria experienced seizures before her first vaccination because, at least in part, there was no "clear evidence."

the fact that a doctor treating Victoria before the vaccination did not diagnose her as suffering from seizures. It appears that the family did not inform the doctors that Victoria was biting her tongue until after the tonic-clonic seizure. See exhibit 11 at 30. More importantly, a retrospective analysis is not surprising. In Dr. Shafrir's second report, he quoted a treatise on neurology, stating, "Patients frequently come to medical attention only after a generalized convulsion, and the history of earlier myoclonic jerks is often obtained retrospectively." Exhibit 85 at 3, quoting exhibit 87 (Eliane Kobayashi et al., Juvenile Myoclonic Epilepsy, in Epilepsy: A Comprehensive Textbook (Jerome Engel & Timothy A. Pedley eds., 2d ed. 2008)). As Dr. Kohrman explained, this is what happened in Victoria's case. Tr. 457-58. Dr. Kohrman's testimony is persuasive.

The finding that Victoria suffered seizures before the October 2, 2007 vaccination does not alter her cause of action. Her cause of action is that a vaccination in 2012 worsened her preexisting epilepsy. Spec. Mstr. Oral Arg. Tr. 604.

On September 4, 2007, Victoria received the meningococcal and tetanus-diphtheria-acellular pertussis vaccines. Exhibit 4 at 2, 3. Mr. Mager has not asserted that either of these vaccines harmed Victoria.

B. Events and Health from the First Dose of the HPV Vaccine (Oct. 2, 2007) to the Second Dose of the HPV Vaccine (Sept. 11, 2012)

Because this period encompasses approximately five years, it is further divided into two subsections.

1. October 2007 to July 2008

Victoria received the HPV vaccine on October 2, 2007. Exhibit 4 at 2, 9. In Mr. Mager's first affidavit, he stated that following the HPV vaccine, Victoria experienced headaches and muscle aches. Exhibit 2 at ¶ 2.

Approximately six weeks after the HPV vaccination, on November 14, 2007, Victoria was attending a funeral. Exhibit 11 at 13. After the funeral while at a restaurant, she experienced a seizure and was taken to the emergency room of Children's Hospital of Wisconsin. Id. at 13, 28. Her extremities shook, her eyes rolled, her face turned blue briefly, and she was disoriented. Id. at 13. In her admission notes, the description of her condition states that she experienced a

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See, e.g., Pet'r's Posthear'g Br. at 54-55 n.20. However, the evidentiary standard for the finding of facts is a mere preponderance.

seizure followed by a second seizure approximately four minutes later. Id. at 28. A head CT scan, urine toxicology screen, and chest x-ray were performed with normal results. Id. at 3-4, 13.

The testifying neurologists differed in how they assessed the funeral. Dr. Kohrman suggested that the stress of attending a funeral for a loved one could have provoked a seizure. Exhibit Z at 2; exhibit BB at 13; Tr. 459-60, 516-17. On the other hand, although Dr. Shafrir agreed that stress can lead to a seizure, he asserted that a funeral is not the type of stressful event that could lead to a seizure within hours. Tr. 329-30.

Dr. Shafrir identified this November 14, 2007 tonic-clonic seizure as the first clinical manifestation of any adverse consequence to the HPV vaccination. Tr. 244. This testimony is consistent with his second report in which he asserted that Victoria "would not have developed epilepsy [had] she not receiv[ed] the vaccination." Exhibit 85 at 6.

The histories given during this hospitalization shed some light on Victoria's health leading up to the tonic-clonic seizure for which she was treated in the hospital. Her father reported that Victoria was a "previously healthy [female] [with] new onset [of seizures]." Exhibit 11 at 19; accord id. at 28 (admitting note stating no history of seizures). Yet, at the same time, the histories also contain details that, as discussed above, contribute to the finding that Victoria had, in fact, had nocturnal seizures before November 14, 2007. For example, the neurology resident or fellow documented that Victoria was having enuresis and an issue with her tongue. Id. at 39-40.

During her hospitalization, Victoria underwent an electroencephalogram ("EEG"). Exhibit 11 at 16-17. The results were abnormal. Id. More specifically, the EEG showed "[i]ntermittent epileptiform spike & slow wave discharges over the left frontal region, as well as the bifrontal region, maximal on left" and "intermittent generalized spike and slow wave discharges, maximum over the left frontal region, seen predominantly during drowsiness and sleep." Id. at 17. It was noted that these discharges "indicate focal sites of cerebral hyperexcitability which can be associated with partial seizures/epilepsy." Id. Dr. Shafrir emphasized that a nationally renowned epileptologist interpreted this EEG as showing discharges in a focal location, not generalized. Tr. 227, 230. Dr. Kohrman responded that a person with primary generalized epilepsy can have intermittent focal discharges "here-and-there, now-and-again." Id. at 447. Dr. Kohrman also maintained that the EEG showed a "classic" pattern for a primary generalized epilepsy. Id. at 517-18.

Late in the evening of November 15, 2007, Mr. Mager requested that Victoria be discharged from the hospital. Exhibit 11 at 36. While the doctors agreed that Victoria could be discharged, they recommended that Victoria take Depakote. Id. Mr. Mager agreed that Victoria would take Depakote for one month. Id. Victoria was expected to follow up with the neurologist who saw her in the hospital, Dr. Sharif, in about one month. See id. at 71.

The medication the doctors prescribed for Victoria, Depakote, is primarily given to patients with generalized epilepsy. Tr. 444-45, 463, 531 (Dr. Kohrman); id. at 557 (Dr. Shafrir). Patients with partial epilepsy are likely to be prescribed levetiracetam (Keppra) or oxcarbazepine (Trileptal). Tr. 463, 531 (Dr. Kohrman); id. at 557-58 (Dr. Shafrir). The doctor's selection of Depakote "push[ed]" Dr. Kohrman to favor a diagnosis of primary generalized epilepsy. Id. at 519.

The day after being discharged from the hospital, Mr. Mager observed Victoria having a similar tonic-clonic generalized seizure while sleeping. Exhibit 6 (Dr. Koehn's notes) at 24. This episode lasted approximately one minute and then she was unconscious for approximately five minutes. Victoria did not remember the event happening. Id. at 24-25.

The follow up appointment happened as expected, on December 12, 2007. Exhibit 11 at 75-77. Dr. Sharif noted that after Victoria was discharged, her parents recalled and reported to Dr. Sharif in this appointment that "for a while, [Victoria] was waking up with big cuts in her tongue at least twice and also complaining of soreness after waking up and it is possible that these might have been seizures." Id. at 75. Victoria's stepmother also reported that there had been no more bedwetting incidents after the prescription of Depakote between her hospital admission and this appointment. Id. Dr. Sharif noted an impression of "focal onset epilepsy by EEG" and "some frontal lobe dysfunction." Id. at 77. Dr. Sharif recommended neuropsychological testing. Id. Dr. Sharif wrote that Victoria might be a candidate for surgery. Id. To Dr. Shafrir, the suggestion that a surgery might improve Victoria's epilepsy meant that Dr. Sharif believed that Victoria's epilepsy was focal. Tr. 230.

Victoria saw another pediatric neurologist, Dr. Monica Koehn, approximately two months later on February 21, 2008. Exhibit 6 at 20. An EEG was performed, the results of which were normal. Id. at 22; accord Tr. 231-32. Referring to the original abnormal EEG taken during her hospital admission, Dr. Koehn noted, "The first EEG pattern could represent a fragment/a more lateralized pattern of an underlying generalized discharge or it could in fact be a focal discharge. Therefore, leaving the possibility open for this to have been a primary or secondarily generalized seizure." Exhibit 6 at 20. Victoria's father and

stepmother requested that she be weaned off Depakote, although the medication appeared to be controlling her seizure activity. Id. at 24, 28. They cited poor performance and difficulties focusing in school, which they thought may have been attributable to the Depakote. Id. at 24. Dr. Koehn therefore directed that she be gradually weaned off Depakote and referred her for neuropsychological testing. Id. at 28; see also Amend. Pet. at ¶ 4. Victoria stopped taking Depakote in March 2008. Exhibit 6 at 9.

On April 1, 2008, Victoria underwent neuropsychological testing with Dr. Stuart Waltonen. Exhibit 6 at 1. Dr. Waltonen noted that she had "a history of some type of learning difficulty at least in the speech and language area." Id. at 6. He also noted a family history of epilepsy and seizures on her maternal side. Id. at 2. With respect to learning and school-related difficulties, he noted that Victoria's stepmother reported "increasing problems with doing well in school" and Victoria's teachers indicated "problems following directions." Id. at 1, 4. Dr. Waltonen ultimately concluded that "[o]verall, her examination does not reveal evidence of significant cognitive impairment with the exception of these very focal language findings." Id. at 6. He further recommended that "her language be looked at a bit more extensively" and, under "Plan," noted, "Refer to the school for speech and language evaluation." Id. at 6-7. Dr. Kohrman indicated that the results of the neuropsychological evaluation showed that Victoria suffered from discrete learning problems and these discrete learning problems are consistent with JME. Tr. 455.

In conjunction with the neuropsychological testing, Victoria saw her neurologist, Dr. Koehn, again. Exhibit 6 at 8. Dr. Koehn noted that discerning the type of seizure Victoria was experiencing was difficult. Id. at 11. When asked about Dr. Koehn's comment, Dr. Shafrir stated that different neurologists did not agree on whether Victoria had "generalized epilepsy, symptomatic generalized epilepsy or partial seizure with secondary generalization." Tr. 341-42. Dr. Kohrman recognized that at the time of Dr. Koehn's assessment, she had limited information about Victoria. Thus, he would have had questions similar to the ones Dr. Koehn raised. Id. at 521.

Dr. Koehn planned to repeat the EEG in the summer when Victoria was not taking Depakote. Exhibit 6 at 11. The next EEG happened on June 26, 2008. It was normal. Id. at 13. Dr. Kohrman stated that the normalized EEG showed that Victoria responded to Depakote. Tr. 464.[8] Dr. Shafrir said that a "total

[8] Dr. Kohrman also opined that the normal EEGs could have missed seizures. Tr. 462.

disappearance of all discharges" would be "quite unusual," although it does happen. Id. at 558.

Dr. Koehn reviewed the EEG in an appointment on July 10, 2008. Exhibit 6 at 15-18. Dr. Koehn documented that Victoria was failing almost all her subjects in school. Id. at 16. The neurologic exam was normal. Id. at 17-18; see also Tr. 521. Dr. Koehn recommended that Victoria continue not taking medication and return in about one year. Exhibit 6 at 18; see also Tr. 342 (Dr. Shafrir's agreement that he would have recommended not continuing medication).

Within one week of the July 10, 2008 appointment with Dr. Koehn, Victoria's stepmother inquired whether the HPV vaccination was related to Victoria's seizures. Exhibit 6 at 19 (call log). Dr. Koehn responded that the HPV immunization was not related to the seizure. Id.

2. July 2008 to September 2012

From July 2008 to September 2012, Victoria attended eighth, ninth, tenth, and eleventh grades. While there is no academic record for Victoria in eighth grade, see exhibit 83, her high school transcript shows her academic performance. Exhibit 83 at 1. During these years, Victoria's grades were mixed, including many Cs and Ds. Id.[9]

During these four years, relatively few medical records were created. A doctor indicated that Victoria was healthy enough to play volleyball in 2009. Exhibit 14 at 1-2.

Victoria established a relationship with a new doctor, Dr. David Budde, on January 5, 2012. Dr. Budde's history indicates that Victoria had not had any seizures in four years. Victoria was not taking any medications. Exhibit 10 at 18.

Victoria returned to Dr. Budde for an annual maintenance exam on March 6, 2012. Id. at 15. Dr. Budde recorded that Victoria was doing "fairly well in school," although there was "room for some improvement." Id. He also noted,

[9] Dr. Shafrir noted that after the seizures initially disappeared, Victoria continued to have problems with learning. Tr. 238. He also opined that "it tells us that the [vaccine] was associated with encephalopathy and was most likely the cause of encephalopathy, the situation." Id.; accord id. at 278. However, Dr. Shafrir appears to overlook that Victoria had difficulties in school before the first HPV vaccination.

"Mother has no concerns about her." Id. The medical record from this visit contains no information about seizures. See id.

Dr. Shafrir emphasized that Victoria was seizure-free for nearly five years. During this period, she likely experienced stress and likely was deprived of sleep at least sometimes. Tr. 215, 338. However, she did not experience seizures. This seizure-free time helps Dr. Shafrir isolate the vaccinations as the triggers for Victoria's seizures.

Dr. Kohrman had less confidence in the assertion that Victoria did not experience seizures during these approximately five years. He noted that after her death, Mr. Mager recounted that Victoria did not always perceive having seizures during sleep. Tr. 491; see also exhibit 13 at 2; exhibit 16 at 3 (Mr. Mager's report to medical examiners).[10]

On September 11, 2012, Victoria received her second HPV vaccination. Exhibit 4 at 1. Mr. Mager alleges that this vaccination aggravated her seizure disorder. Amend. Pet. at ¶ 12; Spec. Mstr. Oral Arg. Tr. 605.

C. Events and Health from October 2012 Until January 2014

Approximately one month after the second HPV vaccination, Victoria was taken to the emergency department of Theda Clark Medical Center on October 10, 2012, after suffering a seizure. Exhibit 7 at 9. Her work-up, including an electrocardiogram ("EKG"), was normal. Id. at 13-14. She was diagnosed with a "probable seizure" and discharged. Id. at 14. When she was discharged, Victoria was recommended to see a neurologist in follow-up. Id. Because Victoria already had a seizure disorder, the doctors at the emergency room did not need to order an EEG. Tr. 525.

It appears that Victoria experienced two other seizures for which she did not seek medical attention emergently. She had a seizure at school on October 19, 2012. Exhibit 9 at 6 (report to Dr. Edgar); exhibit 2 at ¶ 7 (Mr. Mager's first affidavit). She had a third seizure on November 7, 2012. Exhibit 9 at 39 (Dr. Budde's Nov. 8, 2012 report); id. at 6 (report to Dr. Edgar listing seizure on November 8, 2012).

[10] Dr. Kohrman also asserted, "There is no medical record during that period." Tr. 491. However, this assertion overlooks records from Dr. Budde. See id. at 522-23.

Following a third seizure, Victoria saw her primary care doctor, Dr. Budde, on November 8, 2012. Exhibit 9 at 39. At this appointment, she reported two additional seizures following her emergency room visit on October 19, 2012, and November 7, 2012. Id. Dr. Budde recorded that although the doctors at Theda Clark had recommended an appointment with a neurologist, Victoria had not seen one. Id. Dr. Budde noted that Victoria "adamantly denies any drug or alcohol use." Id.

Dr. Budde also stated that Victoria felt "spacy" and may have been "losing some time during lectures or conversations that could represent absence-type seizures." Id. Dr. Kohrman interpreted the history of feeling "spacy" as consistent with Victoria experiencing absence type seizures. Tr. 450. Dr. Shafrir disagreed, stating that feeling "spacy" "is not evidence for absence." Id. at 313.

In the history obtained by Dr. Budde, he wrote, "Sometimes, [Victoria] thinks she can feel them coming on as she will get an unusual sensation. She had a cramping sensation in her calf prior to one seizure." Exhibit 9 at 39. Dr. Shafrir interpreted this information as an "aura." Tr. 232, 309, 559-60. An aura, in turn, makes the diagnosis of JME less likely. Id. In contrast, Dr. Kohrman considered Victoria's unusual sensation (or aura) as consistent with an absence seizure and her cramping as a myoclonic jerk. Id. at 529, 567. At the end of the appointment, Dr. Budde prescribed Depakote and facilitated a referral to a local neurologist, Dr. Terence Edgar. Exhibit 9 at 39.

Victoria saw Dr. Edgar on January 14, 2013. Exhibit 9 at 6-8. Dr. Edgar recorded that "Mom does report occasional staring spells, but it is unclear if there are absence seizures." Id. at 8. Dr. Shafrir relied upon this statement to opine that Victoria did not have absence seizures. Tr. 311-12.

An EEG was also performed. Exhibit 9 at 24-25. Dr. Edgar noted that the "EEG is normal during wakefulness. During sleep there is activation of infrequent potentially epileptiform activity over the left frontal and bioccipital head regions, consistent with the patient's history of generalized seizures." Id. at 25. Dr. Shafrir indicated that the January 2013 EEG supports a diagnosis of partial seizures with secondary generalization. Tr. 347-48. Dr. Kohrman recognized that this EEG was not typical for juvenile myoclonic epilepsy. Id. at 545-46.

Dr. Edgar's impression was a primary generalized seizure disorder and he noted "age of onset at approximately 11 years of age suggests the possibility of juvenile myoclonic epilepsy, although no myoclonic seizures are reported." Exhibit 9 at 8. Dr. Edgar also noted that he "inquired into the myoclonic seizures." Id. He recommended Depakote but, after Victoria specified that she did not wish

to remain on Depakote, Dr. Edgar directed her to begin weaning off Depakote and prescribed a different anti-seizure medication, Keppra. Id. at 8. Dr. Edgar instructed Victoria to follow up in one year. Id. In Dr. Kohrman's opinion, Keppra was likely to be a less effective medication. Tr. 467.

To Dr. Shafrir, Dr. Edgar's record that Victoria did not report myoclonic seizures was important. Victoria could not suffer from JME without having myoclonic seizures. Tr. 232-33. Dr. Kohrman was less concerned about the lack of reports about myoclonic seizures because myoclonic seizures can be difficult to detect. Id. at 443, 451-52, 457-58, 496. Dr. Kohrman gave much more weight to Dr. Edgar's (and Dr. Koehn's) diagnosis of primary generalized epilepsy. Id. at 496; see also exhibit A at 13.

Victoria was supposed to have blood drawn at Berlin Hospital on March 1, 2013. However, she did not appear. Exhibit 9 at 15.

To obtain more information, Dr. Edgar ordered additional labs. On June 18, 2013, Victoria's stepmother told Dr. Edgar that Victoria may miss a dose of Keppra "here and there." Exhibit 9 at 13.

During a follow-up appointment with Dr. Edgar on July 8, 2013, he stated that Victoria's compliance with her Keppra prescription had been "less than ideal," with a subtherapeutic level of the medication in her blood documented from a test on May 30, 2013. Exhibit 9 at 3. Victoria expressed a desire to discontinue use of Keppra, but Dr. Edgar persuaded her to remain on the drug given her history of seizures. Id. at 4. Because Victoria was concerned about not having insurance, Dr. Edgar gave her a three-month supply of Keppra. Id. Dr. Edgar noted "probable juvenile myoclonic epilepsy" at this appointment due to age of onset. Id.[11]

The summer of 2013 was the summer after Victoria had graduated from high school. During her senior year, she earned a mixture of grades. Exhibit 83 at 1. According to Victoria's obituary, Victoria planned to enter military service. Exhibit 110. At Waukesha County Technical College in the fall 2013, Victoria did not earn any credits as she failed two classes and withdrew from a third. Exhibit 82 at 1.

[11] Mr. Mager asserted that "Dr. Edgar only suggests the *possibility* of JME." Pet'r's Posthear'g Br. at 25 (emphasis added). However, Dr. Edgar stated, "The age of onset at 11 years of age suggests *probable* juvenile myoclonic epilepsy." Exhibit 9 at 4, 27 (emphasis added).

In November 2013, Victoria called Dr. Edgar's office to say that she was running out of medication. Exhibit 9 at 11. Due to the lack of records, Dr. Shafrir could not comment on Victoria's compliance with her medication in the fall 2013. Tr. 349-50. According to an account Mr. Mager provided shortly after Victoria's death, she picked up more medication over the holidays. Exhibit 13 at 2. On January 2, 2014, Kathy Mager informed Dr. Edgar's office that Victoria intended to transfer her care to a doctor closer to her, although the doctor was not identified. Exhibit 9 at 9; see also Tr. 355.

Mr. Mager told medical examiners that in November 2013, Victoria was occasionally having seizures in her sleep unknowingly. Exhibit 13 at 2; exhibit 16 at 3; see also Tr. 354. How Mr. Mager reached this conclusion is not clear as it appears that Mr. Mager was not living with Victoria at this time. Tr. 354.

On January 11, 2014, after being discovered unresponsive at a friend's house, Victoria was rushed to the emergency department. Exhibit 8 at 1-2. She was pronounced dead upon her arrival. Id. at 2. As part of an investigation of the death by the Waukesha Police Department, a witness reported that Victoria had been "missing a lot of doses of her medication" and Mr. Mager reported that "she was having seizures more frequently." Exhibit 13 at 2.

An autopsy was performed by Dr. Zelda Okia on January 13, 2014. Exhibit 12 at 1. The findings included pulmonary edema and brain changes consistent with a seizure disorder. Id. at 2; exhibit 16 at 10. Furthermore, a toxicology screen showed levels of Keppra in her blood. Exhibit 13 at 11. According to the toxicology report, regular dosing of Keppra results in 3-37 mcg/mL in the blood, with peak levels of 10-60 mcg/mL within 1.5 hours after dosage. Id. Victoria's toxicology results revealed 26 mcg/mL of Keppra in her blood at the time of death. Id.; see also Tr. 302 (Dr. Shafrir: Victoria did not have low levels of medication in her blood at the time of her death); id. at 467 (Dr. Kohrman: Keppra level of 26 is in the middle of the therapeutic range).

Sections of the brain showed focal areas of subpial gliosis. Exhibit 16 at 16. Gliosis occurs when glial cells cause structural changes to the central nervous system in response to trauma to the brain, such as seizures. Tr. 395-96. Subpial gliosis is found in areas of the brain associated with surface pia, including the superior temporal gyrus and inferior temporal gyrus. Id. at 479-80. All the experts agreed that epileptic seizures can cause gliosis. Id. at 288 (Dr. Shafrir), 394-97, 415 (Dr. Fujinami). Seizures can cause gliosis with or without an inflammatory process. Id. at 289-90.

Beyond those foundational points, gliosis was the topic for a great deal of (conflicting) testimony. See Spec. Mstr. Oral Arg. Tr. 633-37. Dr. Shafrir stated that the amount of gliosis exceeded the amount expected in a person having infrequent seizures. The presence of this excessive gliosis, in turn, meant that Victoria was suffering from a process other than JME. Tr. 287.

Dr. Fujinami noted that the neuropathologist did not report gliosis around the blood vessels in the brain. According to Dr. Fujinami, neuropathologists would report this abnormal finding if they saw it. Tr. 388. From the lack of reporting, Dr. Fujinami inferred that Victoria's blood-brain barrier was intact. Id. A secure blood-brain barrier undermines Dr. Shafrir's theory that an antigen from the periphery disturbed Victoria's central nervous system. Id. at 397. On cross-examination, Mr. Mager's attorney ably pointed out that the record does not contain an actual report from a neuropathologist. Id. at 412-14. Instead, the autopsy simply states that a neuropathologist from Froedert Hospital, Dr. Cochran, reviewed the microscopic slides of the brain. Exhibit 16 at 15. In rebuttal testimony, Dr. Shafrir indicated that there is only one sentence in the autopsy report about gliosis. Thus, deriving any information from it is difficult. Tr. 555-57.

Victoria's death certificate listed "seizure disorder" as her cause of death. Exhibit 1 at 1. The testifying neurologists agreed that Victoria suffered sudden unexpected death in epilepsy ("SUDEP") as a consequence of her epilepsy. Tr. 355 (Dr. Shafrir), 533-34 (Dr. Kohrman adding factors that placed Victoria at greater risk for a sudden and unexpected death); see also Spec. Mstr. Oral Arg. Tr. 648-49.

II. Procedural History

Represented by attorney Mark Krueger, Mr. Mager alleged that a dose of the HPV vaccine given to Victoria on September 11, 2012 "aggravated a prior seizure disorder leading to and causing her death." Amend. Pet. at ¶ 12.[12] He then

[12] The original petition, which was filed roughly two months earlier, had alleged that a dose of the HPV vaccination given on October 2, 2007 caused Victoria's seizure disorder. However, the statute of limitations barred proceeding on a claim based upon the 2007 vaccination. Thus, Mr. Mager's attorney, Mr. Krueger, amended the petition to assert a claim that the 2012 vaccination significantly aggravated the seizure disorder. Although the amended petition also asserts that the 2012 vaccination caused Victoria's seizure disorder, Victoria was already suffering from a seizure disorder before 2012.

gathered medical records, including those requested by the Secretary in advance of the Rule 4(c) report, and the record was complete on February 17, 2015.

The Secretary contested Mr. Mager's entitlement, arguing that Mr. Mager had not established the elements for a significant aggravation claim. Resp't's Rep., filed Apr. 1, 2015, at 8-11. Mr. Krueger withdrew from the case on May 18, 2016. Mr. Mager submitted a fact witness affidavit on July 7, 2015. Ms. Renee Gentry was substituted as counsel of record for Mr. Mager on August 3, 2016, after which the case proceeded to the expert report stage.

Mr. Mager's initial effort to obtain competent reports from experts was not successful. After multiple extensions, Mr. Mager filed his first expert report from Dr. Mikovits and Dr. Ruscetti on November 17, 2016. Eventually, Mr. Mager moved to strike the reports from these partners as well as an expert report from their colleague, Dr. Aliffe. Thus, the details of these reports from people whom Mr. Mager retained are no longer evidence and do not need to be discussed further. However, before Mr. Mager ceased his reliance on Drs. Mikovits, Ruscetti, and Aliffe, the Secretary responded with reports from Dr. Fujinami and Dr. Kohrman on March 2, 2017, and March 22, 2017. While Dr. Fujinami and Dr. Kohrman primarily responded to opinions expressed by Drs. Mikovits, Ruscetti, and Aliffe, Dr. Kohrman presented some opinions that remained relevant after the withdrawal of the earlier reports. Dr. Kohrman asserted that (1) the appropriate diagnosis for Victoria was JME, (2) Victoria's epilepsy began when she was five years old, and (3) Victoria's death was not caused by the HPV vaccination and was more likely related to Victoria's actions before her death, such as failing to take her anti-seizure medication, smoking, drinking beer, and staying up late. Exhibit A at 11-13; see also exhibit Y (Dr. Kohrman's report, dated Mar. 18, 2018) at 2, 7.

In a status conference held on June 19, 2018, the undersigned discussed the relative weaknesses of Mr. Mager's expert reports, and his attorney requested additional time to retain a pediatric neurologist to support his claim better. Mr. Mager then filed an expert report from Dr. Shafrir on October 3, 2018. The presentation of Dr. Shafrir's opinion essentially begins Mr. Mager's development of experts.

In this report, Dr. Shafrir reviewed Victoria's medical history in detail. Exhibit 55 at 1-16. In the course of this summary, Dr. Shafrir raised the potential helpfulness of obtaining the slides from Victoria Mager's autopsy.[13] Id. at 14. Dr.

[13] While Mr. Mager began the process of attempting to obtain the autopsy slides and the exchange of expert reports continued, the case was referred to alternative dispute resolution ("ADR") on January 30, 2019. However, the parties

Shafrir emphasized that Victoria's case was an example of challenge-rechallenge in that she "suffered seizures twice within 1 month of each of her HPV vaccinations." Id. at 16. As for how the HPV vaccination can cause seizures / epilepsy, Dr. Shafrir stated the "mechanism is likely based on molecular mimicry which could be supplemented by activation of the innate immune system." Id. at 20. He asserted that "Victoria had an abnormal immune reaction to the HPV vaccination produced brain inflammation in autoimmune epilepsy." Id.

In response to Dr. Shafrir, the Secretary obtained reports from the people who had previously responded to Drs. Mikovits, Ruscetti, and Aliffe.[14] Dr. Kohrman began, "As I have stated in my previous report Victoria had a preexisting encephalopathy dating to first grade." Exhibit Z at 2. Dr. Kohrman also commented on Victoria's activities just before she died: "when she was prescribed meds, she did not take them regularly prior to her death per Mr. Mager's report. On the night she died she had stayed up until 4 am drinking beer and smoking. Again, her death is associated with a seizure in the face of sleep deprivation." Id.[15]

Dr. Fujinami stated that Dr. Shafrir "is opining that components contained in the vaccine caused an autoimmune epilepsy that resulted in seizures." Exhibit AA at 3. Dr. Fujinami questioned whether Victoria suffered an autoimmune process because "there is no indication of autoimmune indicators being present." Id. Dr. Fujinami also raised doubts about molecular mimicry because one article (Ruiz) showed that peptides from the human papillomavirus "could actually protect from autoimmune neuroinflammation." Id. at 3-4, citing exhibit AA, tab 5 (Pedro J. Ruiz et al., Microbial Epitopes Act as Altered Peptide Ligands to Prevent Experimental Autoimmune Encephalomyelitis, 189 J. Experimental Med. 1275 (1999)).[16]

Given that the Secretary submitted reports from Dr. Kohrman and Dr. Fujinami, the next step was for Mr. Mager to respond. This process was delayed

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failed to reach a settlement agreement and the case was removed from ADR on March 25, 2019.

[14] The reports from Dr. Kohrman and Dr. Fujinami also addressed the most recent reports from Drs. Mikovits, Ruscetti, and Aliffe. But, again, these comments are no longer relevant.

[15] Dr. Kohrman's response to Dr. Shafrir's report was essentially one page.

[16] Like Dr. Kohrman, Dr. Fujinami responded to Dr. Shafrir in essentially one page.

as Mr. Mager attempted to get the autopsy slides. After trying for an extended period to obtain the autopsy slides, Mr. Mager filed a status report on October 28, 2019, stating that a supplemental expert report from Dr. Shafrir would not be necessary. Thus, it appeared that the submission of reports from experts was concluded.

The undersigned issued an order for submissions in advance of potential adjudication on November 20, 2019. This order informed the parties that the case might be decided without a hearing. Order, issued Nov. 20, 2019, at 1. Citing Broekelshen v. Secretary of Health & Human Services, 618 F.3d 1339, 1346 (Fed. Cir. 2010), the undersigned directed the parties to comment upon the appropriate diagnosis for Victoria. This discussion was requested because Dr. Kohrman "proposed that Victoria suffered from juvenile myoclonic epilepsy. . . . While [Dr. Shafrir] seems to be opining that Victoria suffered an encephalopathy and Victoria suffered from an autoimmune epilepsy, not juvenile myoclonic epilepsy." Order, issued Nov. 20, 2019, at 5, citing exhibit A at 13 and exhibit 55 at 18-22. In this context, the parties were instructed to identify the diagnostic criteria for any relevant condition. The parties also were instructed to address the six Loving factors concerning whether a vaccine significantly aggravated an underlying condition. Id. at 6-11. The order also raised, in a separate section, the topic of how Victoria would have been but for the vaccination. Id. at 11.

This order prompted Mr. Mager to obtain another report from Dr. Shafrir, which Mr. Mager filed on July 25, 2020, after receiving multiple extensions. This new report is approximately six pages with another two pages devoted to references. Exhibit 85. Dr. Shafrir began with the "importance of challenge/rechallenge." Id. at 1. Consistent with the November 20, 2019 order, Dr. Shafrir commented upon the appropriate diagnosis. He stated that Victoria "suffered SUDEP [sudden unexpected death in epilepsy] as a result of the acquired autoimmune epilepsy, which was the result of her repeated HPV vaccination." Id. at 2. Dr. Shafrir explained why the diagnosis that Dr. Kohrman proposed, JME, does not fit. Id. at 2-3. Rather, the "basis for the presumed autoimmune epilepsy is the striking relationship of the seizures to the HPV immunization." Id. at 3. Dr. Shafrir also added approximately a dozen articles to support "the role of HPV vaccination in Ms. Mager[']s] autoimmune epilepsy." Id. at 4.

Two days after filing Dr. Shafrir's supplemental report, Mr. Mager made his arguments. Under the topic of "diagnosis," Mr. Mager asserted, "Petitioner contends Victoria suffered from autoimmune epilepsy that resulted in sudden unexpected death with epilepsy." Pet'r's Prehear'g Br., filed July 27, 2020, at 9. After discrediting the diagnosis of JME, Mr. Mager contended that "Victoria's most likely, most appropriate diagnosis would be autoimmune epilepsy." Id. Mr.

Mager presented three ways in which autoimmune epilepsy is typically diagnosed. However, Mr. Mager did not identify any evidence supporting the ways autoimmune epilepsy is typically diagnosed. Id. at 9-10. Mr. Mager asserted, "as demonstrated by Suleiman et al. (Exhibit 88), autoimmune epilepsy can also be present as milder epilepsy cases." Id. at 10.

In introducing his analysis of the Loving factors, Mr. Mager stated, "Petitioner's theory of causation is a neurological autoimmune process triggered by the HPV vaccine, causing autoimmune epilepsy, which is strongly supported by the challenge/ rechallenge." Id. at 16. "Molecular mimicry is the most likely mechanism" by which the HPV vaccine triggered seizures. Id. at 21. Although Mr. Mager discussed aspects of this theory for several pages, he stated, "all of this underpins Petitioner's theory of causation which is based on challenge/rechallenge." Id. at 23. Mr. Mager added that "while he alleges the first HPV [dose] caused Victoria's onset of autoimmune epilepsy, his claim is for the significant aggravation of her epilepsy (largely controlled and seizure-free for five years) by her second dose of HPV. Petitioner is not precluded from using the first dose of HPV vaccination as part of her challenge/rechallenge claim as she is not claiming injury from the initial insult." Id. at 46.

Due to the presentation of a new report from Dr. Shafrir, the Secretary had a chance to respond and did so by filing a report from Dr. Kohrman and a report from Dr. Fujinami. Dr. Kohrman opined about the appropriate diagnosis. He set forth the diagnostic criteria for JME. Exhibit BB at 2. Dr. Kohrman also defined the diagnostic criteria for autoimmune epilepsy. Id. at 11-12. He extensively summarized the events in Victoria's medical history. Id. at 3-10. He concluded, as he did in other reports, that Victoria's seizure disorder is consistent with JME. Id. at 14.

Dr. Kohrman disputed the presence of challenge-rechallenge. He maintained that Victoria's case did not constitute an example of challenge-rechallenge. He explained, "Given the diagnosis of a primary generalized epilepsy, that was never adequately treated [due] to family request and behavior, and the lack of patient taking meds, [h]er history and clinical course cannot be considered a challenge rechallenge. It was never documented medically that she was seizure free prior to [the] second vaccination." Id. at 12.

Dr. Kohrman also maintained, as he had in previous reports, that before the first vaccination Victoria had nocturnal seizures. Id. at 13, citing exhibit 6 at 25 and exhibit 11 at 22. Dr. Kohrman did not address the medical theory that Dr. Shafrir had proposed to explain how a HPV vaccine can aggravate a preexisting seizure disorder. See exhibit BB at 14.

In conjunction with Dr. Kohrman's report, the Secretary also submitted a report from Dr. Fujinami, which is essentially one and a half, single-spaced pages. Dr. Fujinami also disputed whether Victoria's case is an example of challenge-rechallenge. Dr. Fujinami argued "there is no clear information linking the occurrence of seizures to [the] HPV vaccination, let alone an enhanced immune response occurring against the second HPV vaccination due to immunological memory present after the first vaccination with HPV." Exhibit CC at 1.

While Dr. Fujinami recognized that he is not a physician, Dr. Fujinami opined that Victoria "was not consistently taking her anti-seizure medications, which led to the increase of seizures." Id. He also indicated that Victoria did not suffer from autoimmune epilepsy, which was the diagnosis given by Dr. Shafrir. Id.

With the reports from Dr. Kohrman and Dr. Fujinami, the Secretary also filed his brief. A central portion of the Secretary's argument was that Victoria did not suffer from autoimmune epilepsy and that her diagnosis is JME. Resp't's Prehear'g Br., filed Feb. 10, 2021, at 10-15. The basic diagnostic criteria, according to the Secretary and Dr. Kohrman, came from the Higdon and Steriade articles. Id. at 11-12, citing exhibit BB, tab 4 (Lindsay M. Higdon, Autoimmune Epilepsy: More than Just a Paraneoplastic Syndrome, Practical Neurology, Oct. 2018) and exhibit BB, tab 5 (Claude Steriade et al., Acute Symptomatic Seizures Secondary to Autoimmune Encephalitis and Autoimmune-Associated Epilepsy: Conceptual Definitions, 61 Epilepsia 1341 (2020)). In his brief, the Secretary also addressed the Loving prongs. Id. at 17-26.

Mr. Mager replied to the Secretary's arguments. Under the heading, "VICTORIA'S DIAGNOSIS," Mr. Mager asserted that "Victoria suffered from autoimmune epilepsy, which caused SUDEP." Pet'r's Prehear'g Reply, filed Mar. 26, 2021, at 10. He continued, "Victoria suffered from autoimmune epilepsy based on her well-documented systems [sic, "symptoms" might have been intended] and the appropriate diagnostic criteria." Id. With respect to the diagnostic criteria, it appeared that Mr. Mager cited reference 9 in exhibit 65 multiple times. However, that reference was not an exhibit. Mr. Mager also maintained that he satisfied the Loving factors. Id. at 37-50.

Because Mr. Mager had cited, but not filed, reference 9 in exhibit 65, he was directed to file it as an exhibit. Mr. Mager was also instructed to identify "the source of the diagnostic criteria for autoimmune epilepsy." Order, issued June 16, 2021.

In response, Mr. Mager clarified that "Pet. Ex. 65. Ref. 9 . . . does not refer to the ninth reference in Pet. Ex. 65. Rather, Pet. Ex. 65 is also Ref. 09 in Dr. Shafrir's first expert report, filed as Pet. Ex. 55." Pet'r's Status Rep., filed June 17, 2021. For the diagnostic criteria, Mr. Mager stated that "the list itself does not appear – it was derived from Pet. Ex. 88 along with Pet. Ex. 65. The criteria are discussed in that section solely to demonstrate that autoimmune epilepsy can present as milder epilepsy." Id.

The undersigned denied compensation. Decision, 2021 WL 3737056 (Fed. Cl. Spec. Mstr. July 29, 2021). The undersigned found that there was insufficient evidence to support a diagnosis of autoimmune epilepsy. Id. at *11. The undersigned reasoned that Mr. Mager had not met his burden to show either the presence of autoimmune antibodies in Victoria's blood or that Victoria's seizures were refractory. Id. at *7-8, 10. Additionally, the undersigned found that Mr. Mager did not establish that Victoria suffered from autoimmune encephalitis. Id. at *9. Accordingly, since the undersigned found that Mr. Mager did not establish the threshold issue of diagnosis and analysis of causation was therefore unnecessary, compensation was denied. Id. at *11.

Mr. Mager filed a motion for review on August 27, 2021. Mr. Mager argued that the undersigned mischaracterized Victoria's diagnosis. Mot. for Rev., filed Aug. 27, 2021, at 2. He asserted that the undersigned conflated Victoria's pre-death diagnosis and her alleged injury and focused only on autoimmune epilepsy with respect to Dr. Shafrir's causation theory instead of considering the theory in its full context. Id. at 20. Mr. Mager acknowledged that Victoria did not meet the criteria for autoimmune epilepsy but maintained that Victoria's epilepsy was "autoimmune in nature." Id. at 21.

The Court granted Mr. Mager's motion for review and vacated the undersigned's decision denying compensation. Opinion and Order, issued Jan. 21, 2022, at 2, 158 Fed. Cl. 136, 137 (2022). The Court noted that the undersigned was thorough in explaining why Victoria did not have autoimmune epilepsy. Id. at 19, 158 Fed. Cl. at 155. However, the Court concluded that the undersigned mischaracterized Victoria's diagnosis and misunderstood Mr. Mager's argument that "the vaccine caused an autoimmune response triggered recurrence and aggravation of [Victoria's] epilepsy disorder." Id. Accordingly, the case was remanded to the undersigned to consider whether Mr. Mager can satisfy the elements for an off-Table claim under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1278 (Fed. Cir. 2005). Id. at 24, 158 Fed. Cl. at 160.

Following the Court's Opinion and Order, the case was promptly scheduled for a hearing.[17] The hearing was held via videoconferencing over two days, March 8-9, 2022. Dr. Shafrir, Dr. Kohrman, and Dr. Fujinami testified.

After the hearing, the parties argued their positions in briefs, filed on an expedited basis. Mr. Mager submitted his primary brief on March 25, 2022 and his reply on April 5, 2022. In between, the Secretary filed his brief on April 1, 2022. An oral argument was held on April 8, 2022.

III. Standards for Adjudication

A petitioner is required to establish his case by a preponderance of the evidence. 42 U.S.C. § 300aa-13(1)(a). The preponderance of the evidence standard requires a "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 v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing a special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Hum. Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with the dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

As confirmed in W.C. v. Secretary of Health & Human Services, 704 F.3d 1352, 1357 (Fed. Cir. 2013), the elements of an off-Table significant aggravation case were stated in Loving v. Secretary of Health & Human Services, 86 Fed. Cl. 135 (2009). There, the Court blended the test from Althen, which defines off-Table causation cases, with a test from Whitecotton v. Secretary of Health & Human Services, 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resulting test has six components. These 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

[17] The cooperation of the attorneys and witnesses is appreciated.

"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.

Additional details about how to evaluate each prong are provided in the analysis section below.

IV. Analysis

The analysis consists of eight sections. The first section reviews the topic of diagnosis, which is no longer disputed. The next six sections concern the elements of significant aggravation set forth in Loving. Mr. Mager bears the burden of proof on each of these six elements. The final section (section IV.H) considers whether the Secretary has met his burden of proof in showing that Victoria's epilepsy followed the natural course of the disease.

A. Diagnosis

1. Procedural Aspects to Diagnosis and the Parties' Arguments

Among the experts testifying in this case, Dr. Kohrman presented the first opinion regarding diagnosis.[18] He opined that Victoria suffered from juvenile myoclonic epilepsy ("JME"). Exhibit A at 11-13.

In response, Dr. Shafrir disagreed with the opinion that Victoria suffered from JME. Dr. Shafrir opined that "Victoria had an abnormal immune reaction to the HPV vaccination which produced brain inflammation in autoimmune epilepsy." Exhibit 55 at 20. The term "generalized epilepsy" does not appear in Dr. Shafrir's first report. See id. Dr. Shafrir also did not indicate that Victoria's epilepsy was either "mild" or "not severe."

Perceiving a dispute over diagnosis, the undersigned ordered the parties to comment on the condition the HPV vaccination aggravated. Order, issued Nov. 20, 2019, at 5, citing Broekelschen, 618 F.3d at 1346. This direction was based upon a view that Dr. Kohrman had "proposed that Victoria suffered from juvenile

[18] The reports from an earlier set of experts were struck.

myoclonic epilepsy . . . . While [Dr. Shafrir] seems to be opining that Victoria suffered an encephalopathy and Victoria suffered from an autoimmune epilepsy, not juvenile myoclonic epilepsy." Id. The parties were also ordered to identify the diagnostic criteria for any relevant condition.

Mr. Mager filed a second report from Dr. Shafrir. Dr. Shafrir opined that Victoria "suffered SUDEP as a result of the acquired autoimmune epilepsy, which was the result of her repeated HPV vaccination." Exhibit 85 at 2. Dr. Shafrir also indicated that SUDEP "can occur in patients whose epilepsy is not that severe." Id. at 1. Dr. Shafrir, however, did not explicitly state that Victoria's epilepsy was either mild or not severe. Dr. Shafrir added, "The epilepsy diagnosis (not relating to specific etiology) is either secondary generalized epilepsy or symptomatic generalized epilepsy. The etiology of this epilepsy is autoimmune, induced by [an] abnormal immune reaction to the HPV vaccination." Id. at 4.

When Mr. Mager advocated his position, he argued, "Petitioner contends Victoria suffered from autoimmune epilepsy that resulted in sudden unexpected death with epilepsy." Pet'r's Prehear'g Br., filed July 27, 2022, at 9, citing exhibit 55 (Dr. Shafrir's first report) at 18. Mr. Mager further argued that Dr. Shafrir "strongly disagrees" with the assertion that Victoria suffered from JME. Id. Mr. Mager maintained that "Victoria's most likely, most appropriate diagnosis would be autoimmune epilepsy." Id. Mr. Mager also presented three factors by which autoimmune epilepsy "is typically diagnosed." Id. at 9-10. Citing the Suleiman article (exhibit 88), Mr. Mager asserted that "autoimmune epilepsy can also be present as milder epilepsy cases." Id. at 10. In this brief, Mr. Mager did not argue that an analysis of diagnosis pursuant to Broekelschen was inappropriate. See id.

In contrast, the Secretary explicitly argued that whether Mr. Mager had persuasively established that Victoria suffered from JME was a fundamental point. "As the Federal Circuit has made clear, 'the statute places the burden on petitioner to make a showing of at least one defined and recognized injury.'" Resp't's Prehear'g Br., filed Feb. 10, 2022, at 14, quoting Lombardi v. Sec'y of Health & Hum. Servs., 656 F.3d 1343, 1353 (Fed. Cir. 2011). The Secretary further maintained that Victoria did not suffer from autoimmune epilepsy but rather suffered from JME. Id. at 10-15. This position was in accord with Dr. Kohrman's most recent report. See exhibit BB.

Mr. Mager quoted the portion of the Secretary's prehearing brief that cited Broekelschen and Lombardi. Mr. Mager argued that Lombardi was an "unusual" case. Pet'r's' Prehear'g Reply, filed Mar. 26, 2021, at 10, citing Contreras v. Sec'y of Health & Hum. Servs., 107 Fed. Cl. 280, 294 (2012). Otherwise, Mr. Mager advanced the position that "Victoria suffered from autoimmune epilepsy." Id. at

10. Mr. Mager did not qualify this assertion by describing Victoria's epilepsy as either "mild" or "not severe." See id. Concomitantly, Mr. Mager argued that the Secretary "failed to show Victoria suffered from juvenile myoclonic epilepsy." Id. at 16 (capitalization changed without notation).

In response to an order, Mr. Mager provided additional information regarding the diagnostic criteria for autoimmune epilepsy. He stated that the diagnostic criteria in his briefs were derived from two exhibits, exhibits 88 and 65. "The criteria are discussed in that section solely to demonstrate that autoimmune epilepsy can present as milder epilepsy." Pet'r's Status Rep., filed June 16, 2021.

The undersigned found that Mr. Mager asserted that Victoria suffered from autoimmune epilepsy and that Mr. Mager had not persuasively demonstrated that autoimmune epilepsy was an appropriate diagnosis. Decision, issued July 29, 2021. Because this appeared to be a predicate showing, the decision found that Mr. Mager was not entitled to compensation. The decision did not address whether preponderant evidence supported a finding that Victoria suffered from JME. The decision did not quote the portion of the June 16, 2021 status report in which Mr. Mager maintained that "autoimmune epilepsy can present as milder epilepsy."

Mr. Mager challenged this decision by filing a motion for review. In relevant part, he argued that Broekelschen was distinguishable because the parties agreed that Victoria suffered from epilepsy. Pet'r's Mot. for Rev., filed Aug. 27, 2021, at 18.

The Secretary in turn, defended the July 29, 2021 decision. Citing Broekelschen and Lombardi, the Secretary argued that Mr. Mager needed to show the injury (autoimmune epilepsy) that he alleged the HPV vaccine aggravated. Resp't's Resp. to Mot. for Rev., filed Sept. 24, 2021, at 6-7.

The Court granted the motion for review. The Court found that "JME and autoimmune epilepsy are variants of the same disorder—i.e., a seizure disorder." Opinion and Order, at 20, 158 Fed. Cl. at 156. Because the "'existence and nature of the injury' was not in dispute," "the Special Master erred in failing to consider whether the vaccine caused Ms. Mager's injury under Althen and its progeny." Id. at 22, 158 Fed. Cl. at 158. In terms of direction, the Court indicated that "the Special Master must perform the requisite causation analysis under Althen and its progeny." Id.

During the post-remand hearing, the parties continued to develop evidence regarding the type of epilepsy Victoria suffered. Dr. Shafrir stated that Victoria suffered from partial epilepsy with secondary generalizations. Tr. 296, 316; see

also id. at 548-49 (rebuttal testimony). He also explained why, in his opinion, Victoria did not suffer from JME. Id. at 308-14. Dr. Kohrman had the opposite point of view.[19] He stated that Victoria suffered from JME. Id. at 443-69. Dr. Kohrman also discussed why autoimmune epilepsy (or epilepsy with an autoimmune basis) is not an appropriate diagnosis for Victoria. Id. at 471-91.

After the hearing, Mr. Mager's position matched the opinion offered by his expert, Dr. Shafrir. Mr. Mager asserted "that as a result of the HPV vaccination Victoria Mager developed epilepsy which is partial with secondary generalization on an autoimmune basis." Pet'r's Posthear'g Br., filed Mar. 25, 2022, at 18.

2. Resolution

"Upon return of its mandate, the district court cannot give relief beyond the scope of that mandate, but it may act on matters left open by the mandate." Laitram Corp. v. NEC Corp., 115 F.3d 947, 951 (Fed. Cir. 1997) (quoting Caldwell v. Puget Sound Elec. Apprenticeship & Training Tr., 824 F.2d 765, 767 (9th Cir. 1987)) (internal quotation marks omitted). Furthermore, the doctrine of the law of the case, which precludes relitigation of issues explicitly or implicitly decided on appeal, sheds light on implicit appellate considerations of arguments. See Travelers Ins. Co. v. United States, 72 Fed. Cl. 316, 325 (2006) (citing W.L. Gore & Assocs., Inc. v. Garlock, Inc., 842 F.2d 1275, 1278 (Fed. Cir. 1988)) ("The doctrine [of the law of the case], of course, does not constrain a trial court's consideration of an issue that has not been considered on appeal. But the doctrine extends to issues that were implicitly addressed.").

Through the parties' briefs and oral argument, the Court understood their competing positions. Reduced to its simple terms, Mr. Mager's argument was that evaluating whether Victoria suffered autoimmune epilepsy was irrelevant because the parties agreed she had a seizure disorder and his theory for significant aggravation was based on rechallenge. In contrast, the Secretary argued that an Althen analysis is possible only after a determination of whether a vaccinee suffers from a specific condition.

The Court found Victoria had a seizure disorder. Opinion and Order at 20, 158 Fed. Cl. at 156. The Court further ruled the precise type of seizure disorder

[19] Dr. Fujinami also expressed the opinion that Victoria suffered from JME. Tr. 393. However, because Dr. Fujinami is not a medical doctor, his opinion regarding diagnosis merits less weight than the opinion of a neurologist, like Dr. Shafrir or Dr. Kohrman.

did not matter because it found autoimmune epilepsy and juvenile myoclonic epilepsy are on the same spectrum. Id. at 21-22, 158 Fed. Cl. at 157-58. The Court did not remand with instructions to reevaluate whether Victoria suffered from autoimmune epilepsy. The Court also did not remand with instructions to determine, for the first time, whether Victoria suffered JME. The Court remanded for a causation analysis.

Due to this procedural posture, any questions whether Victoria suffered from autoimmune epilepsy, JME, or partial epilepsy with secondary generalizations are not within the scope of remand. The parties agree with this assessment. See Pet'r's Posthear'g Br., filed Mar. 25, 2022, at 28-29; Resp't's Posthear'g Br., filed Apr. 1, 2022, at 55-56. The Court has found the operative diagnosis is "seizure disorder." Thus, the remainder of this discussion uses this term, although another appropriate term might be "epilepsy."

B. Loving Prong One

The first Loving prong is to establish "the person's condition prior to administration of the vaccine." Loving, 86 Fed. Cl. at 144. Here, restating the vaccine at issue is critical.

The operative vaccine is the second dose, which was given on September 11, 2012. Mr. Mager cannot recover compensation based upon the first dose of HPV vaccine, given on October 2, 2007, because Victoria experienced a seizure on November 14, 2007. This November 14, 2007 seizure occurred more than 36 months before Mr. Mager filed his petition. See 42 U.S.C. § 300aa-16(a)(2); cf. Pet'r's Prehear'g Br. at 46 ("Petitioner concedes that he has not alleged injury from the first HPV vaccine . . . .").[20]

Before this vaccine, Victoria had not suffered any seizures in nearly five years. While Dr. Kohrman is correct that, as a matter of logic, Victoria could have had a seizure that no one witnessed and about which Victoria herself was unaware, Tr. 453-54, this argument does not rise to a level of preponderant proof. Victoria's parents appear to have brought her to doctors as needed. When the family saw a doctor, they appeared to try to communicate information about behaviors possibly consistent with a seizure. See Exhibit 6 at 20 (Dr. Koehn's February 21, 2008 report); Exhibit 9 at 39 (Dr. Budde's November 8, 2012 report). The lack of

[20] Mr. Mager has not claimed the statute of limitations for a claim based upon the October 2, 2007 vaccination should be equitably tolled.

medical records reporting seizures for approximately five years tends to show that Victoria was not having seizures, at least at the more likely than not standard.

Although Victoria had not had any seizures in approximately five years before the September 11, 2012 vaccination, five years earlier she did have seizures. As explained above in section I.A, Victoria started having manifestations of her seizure disorder before she received the first HPV vaccination. This finding is based upon all the evidence, including the medical records, affidavits and the reports and testimony of Dr. Shafrir and Dr. Kohrman. Because Victoria's seizures started before the October 2, 2007 HPV vaccination, the first HPV vaccination did not cause the seizure disorder. Locane v. Sec'y of Health & Hum. Servs., 685 F.3d 1375, 1381 (Fed. Cir. 2012); accord Tr. 263. But, this finding carries little consequence to Mr. Mager's case for two reasons. First, as noted above, the October 2, 2007 vaccination is not the basis for Mr. Mager's claim. Second, as discussed more extensively below, Ms. Mager has presented the alternative argument that the first HPV vaccination made her seizure disorder worse. See Tr. 263-64. This worsening, according to Mr. Mager, constitutes a "challenge" event that is one part of the challenge-rechallenge paradigm.

C. Loving Prong Two

The second Loving prong is to find "the person's current condition (or the condition following the vaccination if that is also pertinent)." Loving, 86 Fed. Cl. at 144. After the September 11, 2012 HPV vaccination, Victoria suffered her first seizure in approximately five years on October 10, 2012. Exhibit 7 at 9. She had additional seizures on October 19, 2012 and November 7, 2012. Exhibit 9 at 6 (Dr. Edgar), 39 (Dr. Budde). She was then placed on anti-seizure medications.

Roughly 15 months after the second dose of the vaccination, Victoria died. Exhibit 1 (death certificate). The testifying neurologists agreed that Victoria's death was due to SUDEP. Exhibit 85 at 2; exhibit A at 13; Tr. 355, 533-34.

D. Loving Prong Three

The third Loving prong is to find "whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination." Loving, 86 Fed. Cl. at 144. A "significant aggravation" means "any change for the worse in a preexisting condition which results in a markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4).

Whether any worsening is due to the natural course of Victoria's underlying seizure disorder is not part of this analysis. Sharpe v. Sec'y of Health & Hum.

Servs., 964 F.3d 1072 (Fed. Cir. 2020). Resolution of that issue is deferred to section IV.H, below.

Here, in briefs filed after the hearing, the parties contested this issue stridently. Mr. Mager maintained that before the second HPV vaccination, Victoria "was able to live a normal life" and was "seizure-free for almost five years." Pet'r's Posthear'g Br. at 60-61. Then, after the second vaccination, she experienced seizures "in a greater quantity, frequency, and severity." Id. at 61.

In contrast, the Secretary contended that Victoria "had mild epilepsy before her September 11, 2012, vaccination, and she had mild epilepsy after her September 11, 2012, vaccination." Resp't's Posthear'g Br. at 16-17. The basis for the Secretary's argument regarding the "mildness" of Victoria's epilepsy comes from Dr. Shafrir's testimony. Tr. 238, 344, 561. The Secretary further argued that Victoria's death was not due to any worsening of her epilepsy. Resp't's Posthear'g Br. at 16.

Confronting the Secretary's arguments, Mr. Mager replied more forcefully. He answered: "going from seizure-free for five years, not requiring medication and not being at risk for SUDEP (without seizures, you cannot have SUDEP), to uncontrolled epilepsy, requiring medication, persistent and ongoing seizures, and ultimately death, is a change for the worse in a preexisting condition." Pet'r's Posthear'g Reply, filed Apr. 5, 2022, at 20. Mr. Mager pointed to the abnormal EEG on January 14, 2013 as evidence that Victoria's condition had deteriorated. Id. at 20-21, citing exhibit 9 at 25.

The parties amplified their positions during oral argument. Spec. Mstr. Oral Arg. Tr. 619-20, 627-30 (Mr. Mager), 621-26, 630-31 (the Secretary).

This issue is close. The Secretary's argument that Victoria's epilepsy was mild before the September 11, 2012 vaccination and mild after the September 11, 2012 vaccination has merit. Following the vaccination, Victoria's suffered three seizures, but each seems mild. See exhibit 7 at 9; exhibit 9 at 39 (Dr. Budde's Nov. 8, 2012 report), 6. Then, she went for approximately eight months without having more seizures when she was taking anti-seizure medications. Exhibit 9 at 3 (Dr. Edgar's July 8, 2013 report).

Nevertheless, the evidence preponderates in favor of finding that Victoria's condition was worse than her condition before the vaccination. Before the vaccination, Victoria had not had a seizure in approximately five years and was not taking any anti-seizure medications. Afterwards, Victoria suffered three seizures

within about one month and began taking medications. This deterioration in health constitutes a significant aggravation as defined in 42 U.S.C. § 300aa-33(4).

E. Loving Prong Six / Althen Prong Three

The resolution of the timing prong affects the remaining two prongs. See Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). Thus, this prong is addressed before an evaluation of the theory and logical sequence prongs.

1. Standards for Adjudication

The third Althen prong, which corresponds to the sixth Loving prong, requires the petitioner to show a "proximate temporal relationship" between the vaccination and the alleged injury. Althen, 418 F.3d at 1281. The timing prong of Althen contains two parts. A petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and show that the onset of the disease occurred in this period. Shapiro, 101 Fed. Cl. at 542-43.

2. Parties' Arguments

a) Events in Victoria's Life

With respect to the question of when Victoria experienced observed generalized tonic-clonic seizures after the vaccinations, the parties agree. Victoria received her first HPV vaccination on October 2, 2007, and had her first tonic-clonic seizure on November 14, 2007. Exhibit 3 (vaccination record); exhibit 11 at 13 (emergency department record). The period between these events is 43 days. Tr. 249 (Dr. Shafrir); Pet'r's Prehear'g Br., filed July 27, 2022, at 45.[21]

[21] One reason for finding that Victoria's seizures started before the vaccination was that a medical record created during her hospitalization for November 14, 2007 generalized tonic-clonic seizure indicated that Victoria had questionable events "2 month[s]" and "2 week[s]" earlier. Exhibit 11 at 30; see also footnote 6 above. It seems that to be consistent, if the report of "2 months" is credited, then the report of "2 weeks" also should be credited. And, if the report of "2 weeks" is credited, then Victoria suffered a seizure on October 31, 2007, which is 29 days after the October 2, 2007 vaccination. See exhibit 55 (Dr. Shafrir's first report) at 17 (stating that before the November 14, 2007 tonic-clonic seizure, "there were suggestion[s] that the seizures were occurring earlier").

However, neither party relied upon the report of "2 weeks." Thus, the undersigned will not rule upon an assertion that neither party has made. See Doles

For the second HPV vaccination, the latency is 29 days. Tr. 280 (Dr. Shafrir). Victoria received the second dose on September 11, 2012. Exhibit 3. She experienced a seizure for which she sought treatment at Theda Clark on October 10, 2012. Exhibit 7 at 9.

b) Proximate Temporal Interval

While the parties agree about this chronology, the parties question the appropriate temporal interval. Relying on the Slade post-marketing study (exhibit 59), Dr. Shafrir asserted that Victoria's "seizure occurred within the risk period of 42 days defined by the study." Exhibit 55 at 18.[22] Dr. Shafrir also concluded without elaboration: "The timeframe of the appearance of the seizure and encephalopathy is within the range of other HPV vaccination reaction[s]. It happened twice within the same time range." Id. at 20.

Neither Dr. Kohrman nor Dr. Fujinami questioned the timing in their responsive reports. See exhibits Z and AA. In his first report, Dr. Fujinami noted that nearly 90 million doses of the HPV vaccine were administered in the United States between June 2006 and March 2016. Exhibit I at 3. Among 90 million doses administered, he stated that "there will be overlap with individuals who will present with seizures following vaccination." Id. Dr. Shafrir did not expand upon his opinion regarding timing in his rebuttal report. See exhibit 85. Likewise, the reports from Kohrman and Dr. Fujinami, which were submitted with briefs in advance of adjudication, did not focus on timing. See exhibits BB and CC.

In his brief before remand, Mr. Mager relied on the Slade post-marketing study of HPV vaccinations that showed that the median time between immunization and onset of hypersensitivity reactions was 17 days, with a range of 8-49 days. Pet'r's Prehear'g Br., filed Mar. 25, 2022, at 45, citing exhibit 59 (Barbara A. Slade et al., Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine, Am. Med. Ass'n (2009)) at 754. He emphasized that the Slade study described 4-42 days as "biologically plausible" for onset of transverse myelitis and Guillain-Barré syndrome ("GBS") following the HPV vaccine. Id. Although Mr. Mager acknowledged that onset of autoimmune

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v. Sec'y of Health & Hum. Servs., No. 17-642V, 2022 WL 1231434 (Fed. Cl. Apr. 1, 2022) (granting a motion for review when a special master accepted a theory that petitioner did not assert).

[22] Although Dr. Shafrir asserts that Victoria's seizure occurred within 42 days, the seizure happened on the forty-third day after vaccination.

disorders normally occurs within 3 weeks following the first or second HPV vaccination, he maintained that reports of a three-week onset are "not dispositive." Id.

Initially, the Secretary did not challenge whether 42 days (or 43 days) was an appropriate temporal interval. Instead, the Secretary argued, "Even if the time between Ms. Mager's vaccination and the onset of her epilepsy were considered 'medically acceptable to infer causation-in-fact,' it is well established that temporal proximity is insufficient to establish causation." Resp't's Prehear'g Br., filed Apr. 1, 2022, at 23, citing Moberly, 592 F.3d at 1323 and Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992).

On direct examination during the hearing, Dr. Shafrir's testimony regarding timing was relatively brief, spanning approximately three pages. Tr. 239-42. Again, referencing the Slade post-marketing study, Dr. Shafrir opined that the period of 4-42 days is considered biologically plausible. Id. at 240. Dr. Shafrir added that the Secretary has associated some injuries that occur as long as 42 days after vaccination in the Vaccine Injury Table. Id. at 240.

The Secretary's cross-examination attempted to undermine Dr. Shafrir's opinion. Dr. Shafrir conceded that in his first report, he wrote that "the time interval between the [first] vaccination and the seizure was longer than we typically associate with vaccine side effects." Tr. 250; exhibit 55 at 17. When pressed to explain what immunologic process could be occurring 42 or 43 days after a vaccination, Dr. Shafrir stated that he expected the adaptive immune system (not the innate immune system) would be involved. Tr. 253, 259.

The Secretary further probed Dr. Shafrir's assertion that a 29-day interval would be appropriate for a rechallenge event. Tr. 280-85. Dr. Shafrir had relied upon a paper by Margaret Stanley that measured responses to the HPV vaccinations. Exhibit 68 (Margaret Stanley, HPV – Immune Response to Infection and Vaccination, 5 Infectious Agents and Cancer 19 (2010)). According to this article, "Antigen challenge at 60 months post dose 1 with the quadrivalent vaccine results in a rapid and robust anamnestic response with antibody levels rising within 3-5 days to levels greater than that achieved at peak in the initial immunisation schedule[,] demonstrating the presence of reactive memory B cells." Id. at 22. When asked to explain why Victoria would develop seizures approximately three and a half weeks after the antibodies peaked, Dr. Shafrir did not have a persuasive answer. Tr. 282-84.

Dr. Shafrir fell back to relying upon the Slade study. Tr. 284. Dr. Shafrir indicated that these authors "state that 4 to 42 days is [a] biologically plausible

time interval [for] the appearance of side effects of vaccination." Id. at 285. When pressed to say why the authors found 42 days plausible, Dr. Shafrir testified, "They do not explain." Id. When asked what his opinion is, Dr. Shafrir stated, "I don't have a strong opinion." Id.

Upon redirect, Dr. Shafrir was asked no questions regarding timing. See Tr. 356-57.

The Secretary's challenge to the appropriate temporal interval continued through testimony from Dr. Fujinami. Tr. 400-03. Based upon the Stanley article, Dr. Fujinami indicated that the antibody production in response to a booster dose of the HPV vaccine "occurs within three to five days after that immunization." Id. at 402. Dr. Fujinami, then, reasoned that an anamnestic (or memory) response to a booster dose should occur "within a week after receiving that HPV number 2." Id. at 402-03.

Dr. Fujinami reinforced his opinion by describing what he has observed in his experiments in mice that are induced to develop inflammation within their central nervous systems. In those experiments, the mice develop clinical signs of inflammation about 7-14 days after the initial immunization and then have a "markedly shortened" response after the booster. Tr. 400. Dr. Fujinami did not cite any studies for this proposition.

In Dr. Fujinami's view, the timing of what is predicted by the science does not fit what happened to Victoria, especially for the second vaccination. The interval between the second vaccination and the first seizure after the second vaccination is 29 days. But, to Dr. Fujinami, this much time exceeds what should happen in a rechallenge. Tr. 390. Thus, Victoria's case does not fulfill the challenge-rechallenge paradigm. Id. at 403.

In answering cross-examination questions and questions from the undersigned, Dr. Fujinami defended his position that any rechallenge adverse event would happen sooner than 29 days. Dr. Fujinami stated that literature discussing how primates respond to immunizations shows that clinical disease becomes apparent in 7-14 days. Tr. 418.[23] Because the production of antibodies is one step in the longer process through which antibodies might cross-react and cause damage, the undersigned asked how long the complete process would take. Dr.

[23] While Dr. Fujinami's testimony is not entirely clear about how many vaccinations the animals have received, it seems that Dr. Fujinami is discussing how animals respond to the first (or "priming") dose. Tr. 419.

Fujinami stated that in experimental models using mice, most mice become paralyzed within 14 days. Id. at 420-23.

When asked whether vaccines can cause autoimmune conditions "40-plus days out," Dr. Fujinami acknowledged that some studies have used that window. However, those studies were "very generous." Tr. 419-20.

Dr. Fujinami's opinion concurred with the opinion Dr. Kohrman offered during his testimony. Dr. Kohrman stated that an injury mediated through antibodies would occur within about 7-14 days. Tr. 471-72 (direct testimony), 535 (response to the undersigned's question). He stated that an autoimmune reaction past 40 days is possible, but not likely. Id. at 494 (testimony on cross-examination).

During Dr. Shafrir's rebuttal testimony, he was asked to address whether Victoria's rechallenge event should have occurred earlier. While Dr. Shafrir stated that he "absolutely [did not] agree with" the opinions from the Secretary's experts, Dr. Shafrir did not provide a persuasive explanation. See Tr. 552-54. In this approximately two-page answer, Dr. Shafrir generally maintained that the vaccinations worsened Victoria's seizures. At the end of this response, Dr. Shafrir asserted "it could have happened in six weeks," but did not give any basis for this assertion. Id. at 554.

In their post-hearing briefs, the parties continued to dispute the medically acceptable time. Mr. Mager stated that a petitioner is required to show a "proximate temporal relationship between vaccination and injury." Pet'r's Posthear'g Br. at 33. Citing Paluck v. Secretary of Health & Human Services, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015), Mr. Mager further argued that deadlines should not be "hard and fast." Id.

Mr. Mager argued that Dr. Fujinami's testimony that an immune-driven reaction should take place within approximately two weeks was not persuasive for several reasons. First, Dr. Fujinami did not disclose this opinion in reports before the hearing. Second, Dr. Fujinami's opinion is not consistent with other evidence. The primary inconsistent evidence is the Slade post-marketing study. Pet'r's Posthear'g Br. at 34, 53. The only other article cited in connection with the timing aspect is exhibit 70 (Britain Baker et al., The Safety of Human Papilloma Virus-Blockers and the Risk of Triggering Autoimmune Diseases, 14 Expert Opinion on Drug Safety 1387 (2015)). While this article states the manifestation of symptoms of autoimmunity "normally occurred within the first 3 weeks and following the first or second vaccine injections," exhibit 70 (Baker) at 3, Mr. Mager argues that this statement is "not dispositive." Pet'r's Posthear'g Br. at 34, 53. However, Mr.

Mager did not cite any evidence regarding an expert's view of Baker and it appears that no expert testified about Baker. See Resp't's Posthear'g Br. at 30. Although Dr. Shafrir referenced the Vaccine Injury Table during his testimony (Tr. 295), Mr. Mager did not cite it in his brief as being inconsistent with Dr. Fujinami's opinion.

Mr. Mager's third reason for not crediting Dr. Fujinami's opinion is that his opinion is based upon animal models, not people. Pet'r's Posthear'g Br. at 35, 52. In this context, Mr. Mager questions the usefulness of Dr. Fujinami's opinion because Dr. Fujinami is not a medical doctor. Id. at 35 n.8.

In contrast, the Secretary argued that Mr. Mager's showing regarding timing was not persuasive. Resp't's Posthear'g Br. at 27-37, 53-55. The Secretary maintained that "the injuries and time frames set forth in the Vaccine Injury Table have no bearing on this case." Id. at 27. Later, the Secretary expanded this argument by citing cases in which special masters have rejected the appropriate temporal interval when the injury occurred around the forty-second day after vaccination. Id. at 36-37. The Secretary further argued that the Slade post-marketing study was not persuasive because, in part, "the authors did not explain what made 4 to 42 days plausible for the onset of GBS or transverse myelitis." Id. at 28. In this regard, the Secretary emphasized that when asked why the Slade authors selected this time, Dr. Shafrir did not "supply any basis for his conclusion that 42 days is medically reasonable." Id. at 29, citing Tr. 285. In addition, the Secretary questioned the usefulness of exhibit 70 (Baker), noting that it evaluated a variety of sources including the Vaccine Adverse Event Report System. Id. at 30. Finally, the Secretary argued that Mr. Mager's "exclusive reliance on challenge-rechallenge, without providing any medical theory . . . renders Dr. Shafrir's testimony concerning timing both unreliable and unpersuasive." Id. at 27.

Beyond attacking Dr. Shafrir's opinion regarding timing, the Secretary also defended Dr. Fujinami's view. Procedurally, the Secretary maintained that he could not disclose any opinion from Dr. Fujinami before the hearing because Dr. Shafrir had not disclosed his opinion regarding timing before the hearing. Resp't's Posthear'g Br. at 32-33. Substantively, the Secretary maintained that Dr. Fujinami's experience, including his hypothesis about molecular mimicry being involved in autoimmune disease and work with animal models for epilepsy, made him more qualified than Dr. Shafrir regarding the timeframe for an autoimmune reaction. Id. at 33.

In his post-hearing reply, Mr. Mager again relied on the Slade study, stating that the study establishes 4-42 days as an appropriate time interval between HPV vaccination and onset of symptoms. Pet'r's Posthear'g Br. at 11, citing Tr. 253; exhibit 59 (Slade) at 754. Mr. Mager also reiterated his assertion that the

conclusion in the Baker article that the manifestation of symptoms typically occurs within three weeks after HPV vaccination is "not dispositive." Id. Mr. Mager further stated that although he is not alleging a Table injury, the 2-42-day timeframe contained in the Vaccine Injury Table helps establish a medically acceptable time interval. Id. at 12 n.7. Mr. Mager again argued that appropriate time intervals should not be "hard and fast," and conceded that there "is no definitive timeframe for onset" in this case. Id. at 13.

3. Resolution

Mr. Mager has met his burden. He has persuasively shown that two questions should be answered in his favor. The first (and less important) question is whether 43 days is an appropriate inference for which to infer the first HPV vaccination in 2007 worsened Victoria's preexisting seizure disorder.[24] The second question is whether 29 days is an appropriate interval to infer the 2012 vaccination significantly aggravated a quiescent seizure disorder. On these similar questions, persuasive evidence comes from Slade. When Slade and colleagues were attempting to discover whether the HPV vaccination caused any adverse effects, they used the period of 4 to 42 days as biologically plausible. Exhibit 59 at 754.

While the Slade study, by itself, justifies crediting Dr. Shafrir's opinion regarding timing, some additional support comes from the Vaccine Injury Table. In recommending an association between the flu vaccine and GBS, a peripheral nerve disease, the Secretary "propose[d] an onset interval of 3-42 days." National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table, 80 Fed. Reg. 45,132, 45,146 (proposed July 29, 2015) (codified at 42 C.F.R. pt. 100.3). Special masters have relied upon the Secretary's acceptance of 42 days for flu vaccine-GBS to find an appropriate temporal relationship in other circumstances in some cases. See Mason v. Sec'y of Health & Hum. Servs., No. 17-1383V, 2022 WL 600415, at *25 (Fed. Cl. Spec. Mstr. Feb. 4, 2022) ("[T]he fact that Table claims reflect the Government's reasoned interpretation of persuasive medical science thinking on a causation theory means they can at least be considered in deciding non-Table claims."); Randolph v. Sec'y of Health & Hum. Servs., No. 15-146V, 2021 WL 5816271, at *20 (Fed. Cl. Spec. Mstr. Nov. 12, 2021) ("[T]he GBS 'template' is useful in evaluating Petitioner's success in meeting this Althen prong."). In doing so, special masters have not violated the

[24] Whether 43 days after the first HPV vaccination is an appropriate temporal interval is less important because Mr. Mager's claim is not based upon the first HPV vaccination.

Federal Circuit's direction that "[s]imple similarity to conditions or time periods listed in the Table is not sufficient evidence of causation; evidence in the form of scientific studies or expert medical testimony is necessary to demonstrate causation for such a petitioner." Grant, 956 F.2d at 1148, cited in Resp't's Posthear'g Br. at 27. Here, Mr. Mager has advanced "scientific studies" (the Slade study) and "expert medical testimony" from Dr. Shafrir.

On the other hand, as the Secretary argues, special masters have not universally and uncritically transferred times listed on the Table to cases involving off-Table injuries. See Resp't's Posthear'g Br. at 36, citing Greene v. Sec'y of Health & Hum. Servs., 146 Fed. Cl. 655, 661 (2020) (denying a motion for review of a decision in which the special master found that 41 days was not a medically reasonable interval); Nussman v. Sec'y of Health & Hum. Servs., 83 Fed. Cl. 111, 123 (2008) (denying motion for review of a decision in which the special master found that an appropriate time for the hepatitis B vaccine to cause seizures was 30 days). Those cases undermine, but do not eliminate, the value of the Vaccine Injury Table as supporting Dr. Shafrir's opinion.

From Slade's recognition of 4 to 42 days as biologically plausible, it is a short step of just one additional day to 43 days, which is the amount of time between Victoria's first HPV vaccination and her first generalized tonic-clonic seizure. The Federal Circuit has admonished special masters not to set "hard and fast deadlines." Paluck, 786 F.3d at 1383-84. Thus, the amount of time from Slade may be reasonably expanded to 43 days.

Dr. Fujinami's opinions regarding timing are not credited. First, Dr. Fujinami did not indicate that timing was a problem in his reports. Exhibit I, X, AA, CC.[25] Likewise, the Secretary did not warn that he disputed the timing. See Resp't's Prehear'g Br., filed Feb. 10, 2021, at 22-23.[26] This lack of disclosure is

[25] At best, in response to the (now withdrawn) report from Dr. Mikovits and Dr. Ruscetti, Dr. Fujinami addressed the amount of time for a reaction involving histidine. Exhibit I at 4. But, Dr. Shafrir has not put forward a theory based upon histidine.

[26] The Secretary's excuses regarding the nondisclosure of Dr. Fujinami's opinions are not persuasive. First, the Secretary stated that until Dr. Shafrir testified, Dr. Fujinami did not know when Dr. Shafrir believed Victoria's first seizure occurred. Resp't's Posthear'g Br. at 32. However, Dr. Shafrir linked the first HPV vaccination to Victoria's generalized tonic-clonic seizure on November 14, 2007. See exhibit 55 at 3, 16-17. Second, the Secretary stated that he did not know that Mr. Mager was putting forward 4 to 42 days as a medically reasonable

inconsistent with how the Vaccine Program usually operates. If Mr. Mager had objected to Dr. Fujinami's testimony that an adverse reaction would have occurred within about two weeks, the undersigned most likely would have sustained the objection and struck Dr. Fujinami's testimony. See Simanski v. Sec'y of Health & Hum. Servs., 671 F.3d 1368, 1382 (Fed. Cir. 2012).

Apart from the lack of disclosure, Dr. Fujinami's testimony suffers because he did not present literature supporting his position. Although literature is not required, Althen, 418 F.3d at 1280-81, "a scientific theory that lacks any empirical support will have limited persuasive force." Caves v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 119, 134 (2011), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012). Similarly, the Federal Circuit has recommended that petitioners support expert opinions with medical literature. LaLonde v. Sec'y of Health & Hum. Servs., 746 F.3d 1334, 1341 (Fed. Cir. 2014). This same principle should govern the analysis of opinions that respondent presents.[27]

The Secretary's argument that establishing an appropriate temporal interval requires a medical theory has support from case law. See Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008) (stating that the petitioner must offer a medically acceptable timeframe that coincides with the medical theory of causation under Althen prong one); see also Shapiro, 101 Fed. Cl. at 542. As discussed in section IV.F below, Mr. Mager's medical theory for causation is based on challenge-rechallenge. Since Mr. Mager has established that Victoria's

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time until Mr. Mager presented exhibits 59 and 70 in his prehearing brief. Resp't's Posthear'g Br. at 33. This point is accepted. But, the Secretary did have a chance to respond to the materials presented in Mr. Mager's prehearing brief. With this opportunity, the Secretary presented another report from Dr. Fujinami that did not address timing. See exhibit CC.

[27] On the other hand, in future cases the undersigned might find a properly disclosed and well-supported opinion from Dr. Fujinami persuasive. In determining whether an amount of time is medically appropriate for an inference of causation, the undersigned has considered animal models that attempt to replicate disorders in a person's central nervous system. Contreras v. Sec'y of Health & Human Servs., No. 05-626V, 2012 WL 1441315, at *9-13 (Fed. Cl. Spec. Mstr. Apr. 5, 2012) (lengthy discussion of the time for molecular mimicry), mot. for rev. denied in relevant part after intervening proceedings, 121 Fed. Cl. 230, 246-47 (2015), vacated on other grounds and remanded, 844 F.3d 1363 (Fed. Cir. 2017).

challenge event and rechallenge event occurred within a medically acceptable timeframe, the timing is supported by the medical theory.

Accordingly, for these reasons, Mr. Mager has met his burden of proof regarding Loving prong six. Victoria experienced an aggravation of her preexisting seizure disorder for which she was not taking medications within an appropriate time after the second dose of the HPV vaccination. She also experienced a worsening of her epilepsy after the first dose of the HPV vaccination within a medically appropriate time.

F. Loving Prong Four / Althen Prong One

1. Standards for Adjudication

The first Althen prong requires the petitioner to provide a "sound and reliable" medical theory demonstrating that the vaccine can cause the alleged injury. Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548 (Fed. Cir. 1994)). The petitioner must also offer "a reputable or scientific explanation that pertains specifically to [his] case." Moberly, 592 F.3d at 1322. The petitioner "need not produce medical literature or epidemiologic evidence" to support his theory. Andreu, 596 F.3d 1367, 1379. A petitioner satisfies his burden under prong one when his expert "present[s] a 'biologically plausible' theory." See id. at 1375; see also J. v. Sec'y of Health & Hum. Servs., 155 Fed. Cl. 20, 42-43 (2021).

2. Procedural History and Parties' Arguments

In Dr. Shafrir's first report, he opined that the first HPV vaccination can produce an immune-mediated response, resulting in the development of autoimmune epilepsy. See exhibit 55 at 18, 20. Dr. Shafrir further explained that the second dose leads to an enhanced immune response. See id. at 20. Because Victoria experienced seizures after the first and second doses of the HPV vaccine (and no seizures for nearly five years between vaccinations), Dr. Shafrir opined Victoria's case qualifies as an example of challenge-rechallenge. Id. at 17.

Dr. Shafrir also put forward "[m]echanisms by which Gardasil can produce an autoimmune disease." Exhibit 55 at 19. The most developed mechanism was molecular mimicry, although Dr. Shafrir listed epitope spreading, bystander activation, and polyclonal activation. Id.; see also id. at 20 ("The mechanism is likely based on molecular mimicry . . . .").

The response to Dr. Shafrir's theory came from Dr. Fujinami.[28] In response to Dr. Shafrir's opinion that the HPV vaccine can cause brain inflammation, Dr. Fujinami relied on a study of mice that were injected with peptides, which showed that the "injection of peptides from HPV could actually protect from autoimmune neuroinflammation." Exhibit AA at 3-4, citing exhibit AA, tab 5 (Ruiz).

In addition, in Dr. Fujinami's report that preceded Dr. Shafrir's first report, Dr. Fujinami cited studies about the safety of the HPV vaccine. Dr. Fujinami referenced an article from the Centers for Disease Control and Prevention, which discusses studies from 2012 and 2014. Exhibit I, citing exhibit V (Ctrs. for Disease Control & Prevention, HPV Vaccine Is Safe – (Gardasil) (2016)) at 2. Both studies found that women and girls who received the HPV vaccine "were not more likely to develop autoimmune disorders than those who were unvaccinated." Exhibit V at 2. Dr. Fujinami discussed the studies at the hearing, testifying that "they found no autoimmune signal or . . . association with autoimmune disease." Tr. 375. He added, "there was no indication that there's an increase in seizures in the individuals who were vaccinated with HPV." Id.

Dr. Fujinami also relied on a study that found "no safety signals with respect to autoimmune, neurological, and venous thromboembolic events" among about one million HPV vaccine recipients between ages 10 and 17. Exhibit K (Lisen Arnheim-Dahlstrom et al., Autoimmune, Neurological, and Venous Thromboembolic Adverse Events After Immunisation of Adolescent Girls with Quadrivalent Human Papillomavirus Vaccine in Denmark and Sweden, 347 BMJ 5906 (2013)) at 5.

Dr. Shafrir's second report was similar to his first report. He emphasized the "importance of challenge/rechallenge." Exhibit 85 at 1. Dr. Shafrir referenced a study of autoimmune encephalitis in children, which reported that out of 48 patients with autoimmune encephalitis, three patients received a recent HPV vaccination. Id. at 4, citing exhibit 95 (Yael Hacohen et al., Paediatric Autoimmune Encephalopathies, 84 J. Neurology, Neurosurgery, & Psychiatry 748 (2012)). He also cited a series of articles in which the authors reported people developed autoimmune diseases after a HPV vaccination. Id. at 4-5.

Another study that examined patients with encephalopathy following the HPV vaccination concluded that the patients' responsiveness to immunotherapy suggested an autoimmune mechanism. See exhibit 105 (M. Ando & N. Belonguel,

[28] Dr. Kohrman's report did not meaningfully address the theory by which the HPV vaccine can cause or aggravate seizures. See exhibit Z.

Autoimmune Disorders, 381 J. Neurological Sci. 530 (2017)). However, the authors acknowledged that they could not establish a "direct relationship" between the neurological symptoms and the HPV vaccine. Id.

In conjunction with Dr. Shafrir's second report, Mr. Mager presented written arguments. As a prong-one causation theory, Mr. Mager advanced challenge-rechallenge. See Pet'r's Prehear'g Br. at 19, 23-24; see also exhibit 55 at 17, 20; exhibit 85 at 1. Mr. Mager heavily relied on literature by the World Health Organization ("WHO"), which "defines the relationship between challenge-rechallenge as an adverse reaction to a vaccine as one of *certain causality*." Pet'r's Prehear'g Br. at 24, citing exhibit 57 (World Health Org., Pharmacovigilance Guidelines) at 4.

Mr. Mager argued that "epilepsy can have an immunological mechanism." Pet'r's Prehear'g Br. at 21. To support this theory, Mr. Mager noted that "epilepsy is more common in patients with systemic lupus erythematosus (SLE) who have antiphospholipid antibodies, and it is possible that these antibodies can lead to immune-mediated cortical damage." Id., citing exhibit 64 (Antonio Greco et al., Autoimmune Epilepsy, 15 Autoimmunity Revs. 221 (2016)). He added that "autoimmune antibodies are detected in 9-14% of patients with epilepsy." Id., citing exhibit 64 at 2 and exhibit 88 (Jehan Suleiman et al., Autoantibodies to Neuronal Antigens in Children with New-Onset Seizures, 54 Epilepsia 2091 (2013)).

Mr. Mager relied on the Slade post-marketing study of the HPV vaccine. See Pet'r's Prehear'g Br. at 23, 26, citing exhibit 59 (Slade). The study reports that convulsions made up 8.8% of the serious reported side effects on VAERS reports from June 2001 through December 2008. Exhibit 59 at 752.

Mr. Mager claimed that molecular mimicry was the most probable biological mechanism by which the HPV vaccine can cause epilepsy that is autoimmune in nature. See Pet'r's Prehear'g Br. at 21; Pet'r's Prehear'g Reply at 31. Mr. Mager explained that molecular mimicry "is the cross-reactivity between a foreign-antigen . . . and self-antigens, which induces a break in self-tolerance of the amino acids of the human cells and leads to the immune system attacking its owner's body." Pet'r's Prehear'g Br. at 21, citing exhibit 74 (Nancy Agmon-Levin et al., Vaccines and Autoimmunity, 5 Rheumatology 648 (2009)) at 3. Mr. Mager elaborated that the HPV vaccine "contains viral sequences in L1 protein that are similar to several human proteins integral in regulating immune and neurological function, which set off an autoimmune action triggering [Victoria's] epileptic seizures." Id. at 23.

To support the theory of molecular mimicry, Mr. Mager relied on articles that discuss risks of cross-reactivity with the HPV vaccine. See Pet'r's Prehear'g Br. at 23, citing exhibit 72 (Darja Kanduc, Quantifying the Possible Cross-Reactivity Risk of an HPV16 Vaccine, 8 J. Experimental Therapeutics & Oncology 65 (2009)) and exhibit 73 (Darja Kanduc & Yehuda Shoenfeld, From HBV to HPV: Designing Vaccines for Extensive and Intensive Vaccination Campaigns Worldwide, 11 Autoimmunity Revs. 1054 (2016)). Mr. Mager argued that the articles support the theory of molecular mimicry "by demonstrating six and seven amino acid homologies between the L1 capsid protein of the different strains of HPV included in the Gardasil [vaccine] and human proteins." Id. Mr. Mager added that "the authors identified homologies of the viral vaccine protein and 2 human proteins, the dysfunction of which can cause seizures – calcium sensing reception (CASRO) and perforin (PERF)." Id. Additionally, Mr. Mager argued that this theory is further supported by challenge-rechallenge. See id.

Mr. Mager also referenced a study documenting autoimmune neuromyotonia following the HPV vaccination. See Pet'r's Prehear'g Br. at 20, 43, citing exhibit 107 (Chiara Cerami et al., Autoimmune Neuromyotonia Following Human Papillomavirus Vaccination, Muscle & Nerve, Mar. 2013). Mr. Mager asserted that this study shows that the HPV vaccine can cause brain inflammation and autoimmune neurological conditions. Pet'r's Prehear'g Br. at 20.

With a second chance to address to Dr. Shafrir's theory, Dr. Fujinami responded more directly. He disagreed with Mr. Mager's challenge-rechallenge theory, stating that "there is no clear information linking the occurrence of seizures to [the] HPV vaccination, let alone an enhanced immune response occurring against the second HPV vaccination due to immunological memory present after the first vaccination with HPV." Exhibit CC at 1. Dr. Fujinami also pointed out that Dr. Shafrir had not addressed the study (Ruiz) "where mimicking immunologic epitopes presented in alum [were] reported to protect against neuroinflammation." Id. As to the series of articles that Dr. Shafrir cited, Dr. Fujinami asserted that exhibits 96-108 "are a compilation of case reports . . . and do not relate to seizures/epilepsy let alone autoimmune epilepsy." Id. at 2.

With evidence from Dr. Fujinami, the Secretary disputed Mr. Mager's theory that the HPV vaccine can cause an autoimmune disease. See Resp't's Prehear'g Br. at 19. Citing Dr. Fujinami's report, the Secretary asserted, "There is no evidence that HPV DNA fragments lead to an immune-mediated response and that aluminum at the injection site can cause an autoimmune syndrome." Resp't's Prehear'g Br. at 19, citing exhibit I at 3.

The July 29, 2021 Decision did not address any theory by which a HPV vaccine can cause or aggravate autoimmune epilepsy because it found that Mr. Mager had not established that Victoria suffered from autoimmune epilepsy.

In light of the lack of discussion of a theory or mechanism connecting a HPV vaccine to seizures, the parties' briefs supporting and opposing Mr. Mager's motion for review did not discuss this aspect of the case in any detail. Mr. Mager contended that his "predominant argument was that Victoria experienced challenge/rechallenge." Pet'r's Mot. for Rev., filed Aug. 27, 2021, at 21. He further argued, "Rechallenge is *not* dependent on a finding that Victoria suffered from autoimmune epilepsy." Id.

The Secretary disagreed with this proposition. Shortly after quoting this portion of Mr. Mager's brief, the Secretary argued that "it was necessary and legally correct for the Special Master to undertake a preliminary inquiry regarding whether petitioner met his burden in proving that Ms. Mager suffered from autoimmune epilepsy." Resp't's Resp. to Mot. for Rev., filed Sept. 24, 2021, at 17.

The Court ruled that the approach in the July 27, 2021 Decision was flawed. The "Special Master did not consider petitioner's primary argument; i.e., an autoimmune reaction to the HPV vaccine triggered recurrence and aggravation of Ms. Mager's epilepsy disorder." Opinion and Order at 19, 158 Fed. Cl. at 155. The Court required the special master to "perform the requisite causation analysis under Althen and its progeny." Id. at 22, 158 Fed. Cl. at 158.

In the hearing, Dr. Shafrir and Dr. Fujinami largely testified in accord with the reports they authored. Dr. Shafrir emphasized challenge-rechallenge. He discussed the WHO guidelines, stating that Victoria "clearly meets the criteria for certain side effects caused by the vaccine." Tr. 216. He also reviewed the events in Victoria's life in an attempt to show her history fits the challenge-rechallenge paradigm. Id. at 214-19. Dr. Shafrir also explained that the five-year period of seizure freedom between vaccinations qualifies as a "dechallenge" event, further evidence supporting challenge-rechallenge. Tr. 216-17, 273. On cross-examination, the Secretary questioned whether Dr. Shafrir possessed enough information about Victoria to fulfill the WHO guidelines. These guidelines indicate that an adverse event must take place within a "plausible time." Exhibit 57 at 4; accord Tr. 244, 259. But, by the intimations in his attorney's questions, the Secretary seemed to suggest that the time of events in Victoria's case was not appropriate. See Tr. 259.

When asked about potential biologic mechanisms by which the HPV vaccine can cause or aggravate seizures, Dr. Shafrir stated that molecular mimicry is one

potential mechanism. Tr. 223. He repeated this point on cross-examination, stating that his opinion regarding molecular mimicry is "not a definite certainty . . . . I suggest this is possible, molecular mimicry." Id. at 247. He added other potential mechanisms included a cytokine-driven response, an innocent bystander in the brain's immune system, and "epitope spread." Id. at 247-49. Among these possible theories, the evidence for molecular mimicry "is a little bit stronger than for the other mechanisms." Id. at 249.

Dr. Fujinami's testimony addressed Dr. Shafrir's testimony. Dr. Fujinami explained how repeat vaccinations can enhance the immune response. Tr. 400. However, the challenge-rechallenge paradigm requires appropriate timing. Id. at 403. In this case, Victoria's seizures occurred too long after the vaccinations to be caused by the vaccinations. Id.

Dr. Fujinami also opined that the HPV vaccine has not been shown to increase the incidence of different autoimmune diseases. For example, Dr. Fujinami discussed a short publication from the WHO (exhibit U) that reviewed studies with hundreds of thousands or million participants. These studies did not detect an increase in autoimmune diseases generally and, in some investigations, the authors did not find an increased incidence in seizures specifically. Tr. 371-75. These studies, to Dr. Fujinami, undermined Dr. Shafrir's opinion because if the HPV vaccination could cause a dysregulated immune response, some evidence of that dysregulated immune response would have shown up in these large studies. Id. at 372.

With respect to the possible mechanisms, Dr. Fujinami stated that he did not agree with Dr. Shafrir. For example, on molecular mimicry, Dr. Fujinami pointed out that Dr. Shafrir had not identified what portion of the HPV vaccine would cross-react with a body part leading to epilepsy. Tr. 367. Dr. Fujinami elaborated on his written report's discussion of the Ruiz article to maintain that that the use of a weak adjuvant, like alum, protects against developing an autoimmune reaction. Id. at 367-71, 377-78.

Dr. Fujinami also explained why other potential mechanisms, such as a cytokine-driven reaction, epitope spreading, or bystander activation were not likely. Tr. 365-66, 388-91. His direct testimony concluded with a statement that there is "no connection" between the HPV vaccination and epilepsy. Id. at 403.

After the evidence was completed, Mr. Mager argued his case. He recognized that Althen requires a petitioner to provide "a medical theory connecting the vaccination to the injury." Pet'r's Posthear'g Br., filed Mar. 25, 2022, at 30. However, this "medical theory" differs from a biologic mechanism,

which is not an element of petitioner's case. Id., citing Knudsen, 35 F.3d at 549 and Simanski, 671 F.3d at 1384.

Mr. Mager further argued that establishing challenge-rechallenge satisfies petitioner's obligation to provide a medical theory. Pet'r's Posthear'g Br. at 31-32; Pet'r's Posthear'g Reply, filed Apr. 5, 2022, at 3. A large portion of Mr. Mager's argument under the "Althen prong 1" header consists of contending that Victoria fulfills the challenge-rechallenge paradigm. See Pet'r's Posthear'g Br. at 37-44.

Beyond challenge-rechallenge, Mr. Mager repeated some of his arguments from his prehearing brief. He again asserted, "Molecular mimicry is the most likely mechanism by which Victoria suffered seizures." Pet'r's Posthear'g Br. at 45. Mr. Mager did not raise a theory based on cytokines, epitope spreading, or bystander activation in this brief.

The Secretary disagreed with Mr. Mager's arguments regarding Loving prong four / Althen prong one. On the question of whether invoking the challenge-rechallenge paradigm fulfills the requirement to present a medical theory, the Secretary asserted that Mr. Mager "has not cited any authority in the Vaccine Program that has held that asserting challenge-rechallenge obviates a petitioner's burden to offer reliable evidence of a scientific theory causally connecting the vaccination and the injury." Resp't's Posthear'g Br., filed Apr. 1, 2022, at 17-18. The Secretary also argued that evidence for Victoria experiencing challenge-rechallenge was lacking, primarily due to the problems with timing. See id. at 20-21, 27-34.

As to the potential theories, the Secretary commented that Mr. Mager "made clear his intent to rely exclusively on the challenge-rechallenge paradigm, and elected not to advance any other medical theories of causation." Resp't's Posthear'g Br. at 22, citing Pet'r's Posthear'g Br. at 32-33; accord id. at 21 (Mr. Mager "has declined to endorse any causal theory beyond the challenge-rechallenge paradigm.").[29] The Secretary, thus, made "a truncated response" to questions regarding the plausibility of the different theories Dr. Shafrir mentioned. Id. at 24-25. In conjunction with this response, the Secretary argued, "Several epidemiological studies have demonstrated the absence of increased risk of seizures or epilepsy following HPV vaccination." Id. at 25.

[29] The Secretary did not address Mr. Mager's attempt to distinguish a theory from a mechanism.

3. Resolution

Mr. Mager appears to attempt to satisfy Loving prong four in two respects. First, he offers the challenge-rechallenge paradigm. Second, he offers a hodgepodge of theories, such as molecular mimicry. The former is persuasive and the latter is not.

a) Challenge-Rechallenge

Whether invoking the challenge-rechallenge paradigm constitutes a "theory" depends, at least in part, on the meaning of the phrase "a medical theory causally connecting the vaccination and the injury" from Althen, 418 F.3d at 1278. The interpretation of a case is a question of law, which appellate authorities review de novo. Alcon Research Ltd. v. Barr Laboratories, Inc., 745 F.3d 1180, 1190 (Fed. Cir. 2014); Toro Co. v. White Consolidated Industries, Inc., 383 F.3d 1326, 1330 (Fed. Cir. 2004).

Here, there appears to be no controlling precedent that answered the specific question of whether challenge-rechallenge constitutes a theory. However, the appellate authorities seem inclined to accept challenge-rechallenge as a theory.

In assessing challenge-rechallenge, a starting point is Capizzano. In the special master's underlying decision, he found that the hepatitis B vaccine can cause rheumatoid arthritis. Thus, he effectively found that the petitioner had met her burden regarding the first Althen prong. Capizzano, 440 F.3d at 1325. Thus, as the Secretary argues, the Federal Circuit "did not discuss whether the challenge-rechallenge paradigm is sufficient by itself to satisfy Althen prong 1." Resp't's Posthear'g Br. at 18.[30] For the issue that the Federal Circuit did confront, whether the petitioner had met her burden of proof on prong two, the Federal Circuit recognized that challenge-rechallenge evidence could be probative of causation. Capizzano, 440 F.3d at 1327.

Subsequently, in evaluating whether reasonable basis supported the claims set forth in a petition, the Federal Circuit stated that "the occurrence of a challenge-rechallenge event . . . has been recognized as a basis for establishing causation." James-Cornelius v. Sec'y of Health & Hum. Servs., 984 F.3d 1374, 1381 (Fed. Cir. 2021) (citing Capizzano, 440 F.3d at 1322). While the sentence in James-

[30] This lack of analysis from the Federal Circuit on prong one, in turn, allowed for a different finding on prong one based upon different evidence. See Bean-Sasser v. Sec'y of Health & Hum. Servs., 127 Fed. Cl. 161, 167-68 (2016).

Cornelius does not specify whether the challenge-rechallenge occurrence is part of Althen prong one or Althen prong two, that analytic structure does not matter.

Althen prong two has been likened to asking whether the vaccine did cause the injury. Evidence that a vaccine did cause an injury must imply that the vaccine can cause the injury. "When a treating physician concludes that an injury or illness was caused by a vaccine, that conclusion is circumstantial evidence that the vaccine did in fact cause that injury or illness." Caves, 100 Fed. Cl. at 136.

Thus, the undersigned holds that persuasive proof that a vaccinee experienced challenge-rechallenge satisfies a petitioner's burden to present a theory causally connecting a vaccine to an injury. See Waterman v. Sec'y of Health & Hum. Servs., No. 13-44V, 2016 WL 761173, at *7-8 (Fed. Cl. Spec. Mstr. Feb. 5, 2016) (ruling finding entitlement to compensation based, in part, on the special master's finding that the petitioner demonstrated challenge-rechallenge).

The ensuing question, then, is whether Mr. Mager has shown with preponderant evidence that Victoria experienced challenge-rechallenge. The short answer is yes.

The Secretary's argument against challenge-rechallenge is that the timing does not fit. See Resp't's Posthear'g Br. at 19-22; Spec. Mstr. Oral Arg. Tr. 660. However, for reasons explained in section IV.E, above, Mr. Mager has met his burden regarding timing.

The basic chronology shows how Victoria experienced worse seizures within an appropriate amount of time after the vaccinations to conclude that she experienced challenge-rechallenge.

Date	Event
9/14/2007	Approximate onset of tongue biting, which is evidence of a seizure. In addition, by this time, Victoria was having episodes of bedwetting.
10/2/2007	First HPV vaccination.
11/14/2007	First generalized tonic-clonic seizure.
	A nearly five-year period in which no seizures are reported, consistent with Dr. Shafrir's opinion on dechallenge.

9/11/2012	Second HPV vaccination.
10/12/2012	The first of three seizures, leading to a prescription for anti-seizure medication.

Accordingly, Mr. Mager has met his burden on Loving prong four (Althen prong one) due to the preponderant proof of challenge-rechallenge.

b) Other Theories

As noted previously, whether a demonstration of challenge-rechallenge satisfies an obligation to present a medical theory causally connecting the vaccine with the injury has not been directly addressed by an appellate authority. To avoid the need for a potential remand, the undersigned discusses Mr. Mager's alternative methods for establishing Loving prong four.

Mr. Mager's evidence as to how the HPV vaccine can aggravate a preexisting seizure disorder is not persuasive. Among the different theories Mr. Mager advanced, Mr. Mager identified molecular mimicry as "most likely." Pet'r's Posthear'g Br. at 45. However, Mr. Mager has not shown that Dr. Shafrir's opinion how the HPV vaccine can cause (or aggravate) seizures is reliable.

Mr. Mager has shown that the HPV vaccine prompts human beings to produce an immune response, including the production of antibodies. Exhibit 68. Mr. Mager has also shown that portions of a vaccine might resemble (or mimic) portions of human tissue. See exhibit 74.

But, Mr. Mager has not persuasively linked the production of antibodies to the development of epilepsy. While Dr. Shafrir stated that antibodies are "known" to cause autoimmune epilepsy, Tr. 224, Dr. Shafrir later retreated from this statement. The presence of antibodies in patients with epilepsy was not statistically different from the presence of antibodies in controls. Id. at 305-07 (discussion of exhibit 88 (Suleiman)). Furthermore, while Mr. Mager cites to a series of articles, Pet'r's Posthear'g Br. at 46, he elicited no significant testimony about those articles. The lack of testimony is not surprising as those articles discuss conditions other than epilepsy. See exhibit CC (Dr. Fujinami's report) at 1-2. While the undersigned has considered those articles, Mr. Mager has not persuasively shown how they are relevant to the theory.

On cross-examination, Dr. Shafrir testified "molecular mimicry is a possibility." Tr. 245.[31] This description is apt. A theory that is "possible" does not meet a petitioner's burden of proof. Moberly, 592 F.3d at 1322.

As for the remaining theories, Mr. Mager has done even less to support them. For example, although the Secretary elicited testimony from Dr. Shafrir about cytokines, bystander activation, and epitope spreading, Tr. 247-49, Mr. Mager did not advance those theories. Neither "cytokine" nor "bystander" nor "epitope spreading" appears in Mr. Mager's post-hearing brief. In any event, Dr. Fujinami easily and persuasively demonstrated weaknesses in Dr. Shafrir's testimony. Id. at 365-71, 386-98.

In conjunction with this testimony, Dr. Fujinami discussed epidemiological studies, which his earlier reports had cited. Tr. 365-77. These studies did not detect any increase in various diseases after HPV vaccination.[32] For a lengthy discussion of the value of epidemiologic studies in the Vaccine Program, see Tullio v. Sec'y of Health & Human Servs., No. 15-51V, 2019 WL 7580149, at *5-8 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448, 475 (2020).

Consequently, if challenge-rechallenge were not a way to satisfy the requirement to present a theory, then Mr. Mager would not have met his burden of proof regarding Loving prong four (corresponding to Althen prong one).

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[31] The transcript may contain an error at this point. The entire sentence as transcribed reads: "Differently molecular mimicry is a possibility." Dr. Shafrir may have actually stated "Definitely molecular mimicry is a possibility." Regardless of the first word, Dr. Shafrir said "molecular mimicry is a possibility."

[32] Studies included exhibit U (World Health Org., 89 Weekly Epidemiological Record 53 (2014)); exhibit M (C. Chao et al., Surveillance of Autoimmune Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine, 271 J. Internal Med. 193 (2011)); exhibit V (Ctrs. for Disease Control & Prevention, HPV Vaccine Is Safe – (Gardasil) (2016)); exhibit AA, tab 5 (Pedro J. Ruiz et al., Microbial Epitopes Act as Altered Peptide Ligands to Prevent Experimental Autoimmune Encephalomyelitis, 189 J. Experimental Med. 1275 (1999)).

G. Loving Prong Five / Althen Prong Two

1. Standards for Adjudication

The second Althen prong requires a petitioner to show a logical sequence of cause and effect usually supported by the medical records. Althen, 418 F.3d at 1278; Capizzano, 440 F.3d at 1326. The Federal Circuit has instructed special masters to consider carefully the views of a treating doctor, "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.'" Capizzano, 440 F.3d at 1326.

2. Parties' Arguments

In briefing before remand, Mr. Mager argued that Victoria experienced challenge-rechallenge, meaning she experienced seizures following both HPV vaccinations. Pet'r's Prehear'g Br. at 44. Mr. Mager further explained that she experienced a five-year period of seizure freedom in between in her first and second HPV vaccinations. Id. Mr. Mager argued that challenge-rechallenge supports a logical sequence of cause and effect. See id. Dr. Shafrir wrote in his first report, "Victoria's immune system ha[d] been primed and then reactivated for [a] more pronounced immune reaction to the vaccine." Exhibit 55 at 20.

Additionally, with respect to prong two, Dr. Shafrir opined in his supplemental report that the subpial gliosis found in Victoria's autopsy suggests chronic brain inflammation. Exhibit 85 at 4. This is consistent with Dr. Shafrir's testimony during the hearing. Tr. 287.

Dr. Shafrir opined in his supplemental report that the finding of subpial gliosis in Victoria's autopsy indicated that she likely had chronic neuroinflammation. Exhibit 85 at 4. Dr. Shafrir reiterated this opinion at the hearing. Tr. 287. He elaborated that neuroinflammation can cause gliosis. Id. at 289.

Conversely, the Secretary argued that the record does not support a logical sequence of cause and effect because there is "no indication 'of autoimmune indicators being present.'" Resp't's Prehear'g Br. at 21, citing exhibit AA at 3. Both Dr. Fujinami and Dr. Kohrman addressed Dr. Shafrir's opinion regarding subpial gliosis and chronic brain inflammation in their reports. See exhibit A at 14; exhibit AA at 4. Dr. Fujinami stated that "just the act of having seizures can cause gliosis." Exhibit AA at 4. He added, "One does not have to hypothesize that [the] HPV vaccination causes gliosis when individuals with epilepsy already have

gliosis." Id. Dr. Fujinami reiterated his opinion that seizures can cause gliosis during the hearing. Tr. 394.

Dr. Kohrman opined that the finding of gliosis in Victoria's temporal lobe was caused by her seizures. Exhibit A at 14. He stated, "There was no evidence of acute or chronic inflammation documented at the time of autopsy." Id. He noted that Victoria's lab work on May 30, 2012, showed a normal white blood cell count and "the eosinophils and basophils were only slightly [above] the upper limits of normal." Id.; see also exhibit 9 at 21-22. Dr. Kohrman asserted that these results do not suggest inflammation in the central nervous system. Exhibit A at 14. He added that Victoria's MRI after her first seizure was normal and did not show any flair changes, which would have been indicative of inflammation. Id. at 12. This was consistent with Dr. Kohrman's testimony at the hearing.

Dr. Kohrman also disputed Dr. Shafrir's theory regarding brain inflammation. In his first report, Dr. Kohrman stated that Victoria's "MRI shortly after [her] first seizure was normal with no evidence of changes on flair studies. Flair changes are sensitive to blood brain barrier breakdown that can be associated with brain inflammation." Exhibit A at 12. Similarly, at the hearing, Dr. Kohrman testified, "I would expect [Victoria's] MRI to have shown [flair] and T2 changes, none of which were present." Tr. 482. He characterized flair and T2 changes as "the hallmark of inflammation." Id. During his rebuttal testimony, Dr. Shafrir agreed with Dr. Kohrman that if Victoria's seizures were caused by neuroinflammation, her MRI would have shown flair and T2 changes. Id. at 562-63.

Dr. Fujinami also argued that Victoria's seizures were more likely the result of poor compliance with her anti-seizure medication. Exhibit CC at 1. Dr. Fujinami referenced an article about JME, which states that JME patients can control their seizures with "relatively low doses of appropriate anticonvulsants." Id., citing exhibit 86 (James Selph, Juvenile Myoclonic Epilepsy, Medscape (June 24, 2016)) at 3.

3. Resolution

Here, there is no dispute that challenge-rechallenge can show that a vaccine harmed a person and then, on re-exposure, harmed the person again. Capizzano, 440 F.3d at 1322. As explained in the previous section, Mr. Mager has shown this sequence of events for Victoria. Thus, an inference of causation is appropriate.

Capizzano also teaches that the views of treating doctors merit consideration. 440 F.3d at 1326. Here, the most direct statement from a treating

doctor came from Dr. Koehn in July 2008. In an exchange of telephone messages with Victoria's stepmother, Dr. Koehn communicated that the HPV vaccination was not related to the seizure. Exhibit 6 at 19 (call log). This statement, however, does not dictate a finding against Mr. Mager because any statement from a treating doctor does not bind a special master. 42 U.S.C. § 300aa-13(b)(1); see also Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.67 (2009). Dr. Koehn's July 2008 statement carries less weight because Dr. Koehn expressed this opinion before Victoria received her second HPV vaccination. Thus, in a way, Dr. Koehn's opinion was based upon incomplete information.

Accordingly, Mr. Mager has met his burden of proof for Loving prong five.

H. Natural Course of Underlying Disorder

Mr. Mager has demonstrated a prima facie case that the 2012 vaccination significantly aggravated Victoria's preexisting epilepsy. He is entitled to compensation unless the Secretary can show some other factor caused Victoria's injury. 42 U.S.C. § 300aa-13(a)(1)(B). For a significant aggravation case, the Secretary bears the burden of showing that the vaccinee's post-vaccination condition was consistent with the natural course of the vaccinee's preexisting problem.

Here, the Secretary has not carried his burden. The Secretary's argument seems premised, at least in part, on an assertion that Victoria suffered from juvenile myoclonic epilepsy. See Resp't's Prehear'g Br. at 25; Resp't's Posthear'g Br. at 60; Spec. Mstr. Oral Arg. Tr. 688-89. This argument is difficult to credit after the Court determined that the relevant condition is simply epilepsy. See Resp't's Posthear'g Br. at 55-56.

The parties did not extensively discuss the natural course of generic epilepsy in their briefs and the evidence on this point seems paltry. Through Dr. Kohrman, the Secretary persuasively showed that a person with JME and who is not taking anti-seizure medication may have years without seizures and then redevelop seizures. Tr. 456, discussing exhibit BB-2 (Iris E. Martinez-Juarez et al., Juvenile Myoclonic Epilepsy Subsyndromes: Family Studies and Long-Term Follow-Up, 129 Brain 1269 (2006)), 466, 489-90. Thus, the Secretary possessed a good-faith basis for arguing that Victoria's course was coincident to, and not aggravated by, the two HPV vaccinations. This argument, however, is outweighed by the value of challenge-rechallenge.

A secondary argument from the Secretary is that Victoria's death was due to the natural course of her epilepsy. See Resp't's Posthear'g Br. at 15-17. Several

points underlie this argument. First, as found in section I.A above, Victoria suffered from seizures before the initial dose of the HPV vaccination. Thus, the HPV vaccination did not cause her epilepsy. Second, people whose epilepsies are controlled without medication can redevelop seizures unpredictably. See exhibit F (Julia Hofler et al., Seizure Outcome in 175 Patients with Juvenile Myoclonic Epilepsy – A Long-Term Observational Study, 108 Epilepsy Rsch. 1817 (2014)) at 1820 (observing that 16 out of 175 JME patients experienced two years of seizure freedom without taking antiepileptic medications); see also Tr. 492 (Dr. Kohrman's testimony that periods of seizure freedom are common in patients with JME). Third, Victoria had "reluctance to remain on Depakote (an effective treatment for her generalized seizures)" and she "lack[ed] compliance with Keppra (a less effective treatment for generalized seizures)." Resp't's Posthear'g Br. at 16.

To this list, the Secretary added testimony from Dr. Shafrir. Dr. Shafrir stated that risk factors for sudden unexplained death in epilepsy ("SUDEP") include nocturnal seizures, generalized seizures, poorly controlled seizures, and poor compliance. Tr. 331-32. But, regardless of risk factors, "SUDEP could have occurred after a few months with epilepsy, could have occurred after 20 years of epilepsy." Id. at 355. To Dr. Shafrir, Victoria's "SUDEP is not correlated to the vaccine or anything else." Tr. 355. The Secretary emphasizes Dr. Shafrir's "not correlated" comment. Resp't's Posthear'g Br. at 16-17.

Mr. Mager's response is to cite Dr. Kohrman's testimony that before Victoria's death, her epilepsy was "uncontrolled." Pet'r's Posthear'g Reply at 19, citing Tr. 534. However, characterizing Victoria's epilepsy in the months before her death in January 2014 as "uncontrolled" does not mean that the vaccination approximately one year earlier made the seizures uncontrolled. Dr. Shafrir testified that Victoria's "death may have not happened if she was able to get better treatment." Tr. 355. A relevant factor is that Victoria may have had poor compliance with her medication. See exhibit 13 at 2 (witness report that Victoria had been missing doses of her medication prior to her death). However, according to a toxicology report, Victoria had therapeutic levels of Keppra in her blood at the time of her death. Id. at 11; Tr. 302 (Dr. Shafrir), 467 (Dr. Kohrman).

Mr. Mager further maintained that although Dr. Shafrir did not correlate Victoria's death with the HPV vaccination, he correlated her death with epilepsy. Spec. Mstr. Oral Arg. Tr. 647. Mr. Mager argued, SUDEP "is directly related to [Victoria's] seizures," and her seizures were "directly related to the vaccine." Id. He added that Victoria's epilepsy was uncontrolled after her second HPV vaccination, and her resulting condition cannot be separated from her subsequent death. Id. at 672-74.

This issue, too, is close. A potentially useful piece of information would have been how often people with mild epilepsy experience SUDEP. This evidence could have informed an assessment of how Victoria's epilepsy, unaggravated by the second HPV vaccination, might have progressed.

Without this evidence, the claim that Victoria's death is the natural result of her epilepsy seems possible. But, the Secretary has not established this argument by a preponderance of the evidence.

V. Conclusion

Accordingly, Mr. Mager has established that the September 11, 2012 HPV vaccination significantly aggravated Victoria's epilepsy and caused her death. Therefore, he is entitled to compensation under the Vaccine Act. Pursuant to Vaccine Rule 28.1(a), the Clerk is directed to notify the Court of this decision.

An order regarding damages will be issued shortly.

IT IS SO ORDERED.

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