Corrected

In the United States Court of Federal Claims

No. 14-820
(Filed: 20 June 2023*)

MICHAEL MAGER, as parent of VICTORIA MAGER,	*
Petitioner,	*
v.	*
SECRETARY OF HEALTH AND HUMAN SERVICES,	*
Respondent.	*

Renee J. Gentry, Vaccine Injury Clinic, George Washington University Law School, of Washington, DC, for petitioner.

Zoe Wade, Trial Attorney, with whom were *Darryl R. Wishard*, Assistant Director, *Heather L. Pearlman*, Deputy Director, *C. Salvatore D'Alessio*, Director, Torts Branch, *Brian M. Boynton*, Principal Deputy Assistant Attorney General, Civil Division, Department of Justice, all of Washington, DC, for respondent.

OPINION AND ORDER

HOLTE, Judge.

"[W]hile most of the Nation's children enjoy greater benefit from immunization programs, a small but significant number have been gravely injured." *Cloer v. Sec'y of Health & Hum. Servs.*, 654 F.3d 1322, 1325 (Fed. Cir. 2011) (quoting H.R. Rep. No. 99-908, at 4 (1986)). The Vaccine Act "assure[s] parents that when their children are the victims of an appropriate and rational national policy, a compassionate [g]overnment will assist them in their hour of need." *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1364 (Fed. Cir. 2019) (Newman, J., dissenting) (quoting statement of Sen. Edward Kennedy, S. Comm. on Labor & Human Res.). The pro-petitioner Vaccine Act does not require clarity or perfection in proving a vaccine injury. Indeed, "'[t]he purpose of the Vaccine Act's preponderance standard is to allow

* This Opinion and Order was initially filed under seal on 2 June 2023 pursuant to Vaccine Rule 18(b) of the Rules of the Court of Federal Claims ("VRCFC"). The Court provided the parties 14 days to submit proposed redactions, if any, before the Opinion and Order was released for publication. Neither party proposed redactions nor indicated there were no redactions by 16 June 2023, the 14-day deadline. This Opinion and Order is now reissued for publication in its original form.

the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body,' even if the possible link between the vaccine and the injury is 'hitherto unproven.'" *Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1261 (Fed. Cir. 2011) (quoting *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005)).

The current issue before the Court revolves around challenge-rechallenge—an inferred clinical determination of causality, generally accepted in the medical field and based on repeat adverse reactions to the administration of a pharmaceutical or biologic. Victoria Mager's first observed seizure occurred shortly after receiving the first dose of the HPV vaccine. The seizures subsided for several years until Ms. Mager received a second dose of the HPV vaccine, at which point her seizures returned—ultimately resulting in her death. Petitioner proffered the challenge-rechallenge paradigm as evidence of causation, and the Special Master found Mr. Mager was entitled to compensation under the Vaccine Act. Respondent moved the Court for review of the Special Master's Ruling Finding Entitlement alleging the Special Master erred by allowing the use of the challenge-rechallenge paradigm, among other things. The Court addresses some nuances of challenge-rechallenge as it applies to the Vaccine Act. For the following reasons, the Court denies respondent's Motion for Review.

I. Petitioner's Medical History and the Vaccination

The Court's recitation of the background facts draws from the Special Master's Decision Denying Compensation, ECF No. 189, the Court's Opinion and Order granting petitioner's 2021 Motion for Review, *Mager v. Sec'y of Health & Hum. Servs.*, 158 Fed. Cl. 136 (2022), ECF No. 202, and the Special Master's Ruling Finding Entitlement to Compensation ("Ruling Finding Entitlement"), ECF No. 224.

> Ms. Mager's health history was relatively normal before receiving the vaccination for the human papilloma virus ("HPV").[1] Ms. Mager received the vaccine on 2 October 2007. Pet. at 1, ECF No. 1. Six weeks later, Ms. Mager suffered a seizure and was taken to a nearby emergency room. Pet'r's Ex. 11 at 28, ECF No. 9-4. The admission notes from that visit state she experienced a seizure followed by a second seizure approximately four minutes later. *Id.* Her head CT scan, urine toxicology screen, and chest x-ray were all normal. *Id.* at 3–4, 13. An electroencephalogram ("EEG") "indicate[d] focal sites of cerebral hyperexcitability which can be associated with partial seizures/epilepsy." *Id.* at 17. Ms. Mager was prescribed Depakote, an anti-seizure medication, and discharged on 15 November 2007. *Id.* at 38.
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> In a follow-up visit on 12 December 2007, Ms. Mager's physician, Dr. Shafrir, noted that her parents recalled that "for a while [after her initial seizure], [Ms. Mager] was waking up with big cuts in her tongue at least twice and also

[1] Prior to remand, "the Special Master made no finding concerning when [Ms. Mager's] seizures began." *Mager*, 158 Fed. Cl. at 2 n.1. On remand, the Special Master found the following two factors persuasive: (1) Dr. Kohrman's testimony asserting the cessation of Ms. Mager's enuresis upon taking anti-seizure medication was evidence of seizures occurring prior to receiving the first HPV vaccine; and (2) various medical records pointing to the existence of tongue-biting episodes prior to receiving the first HPV vaccine. Ruling Finding Entitlement at 4–6.

complaining of soreness after waking up and it is possible that these might have been seizures." Pet'r's Ex. 11 at 75. Ms. Mager's stepmother also reported Ms. Mager's enuresis was resolved after she began taking her anti[-]seizure medication, Depakote. *Id.* Dr. Shafrir noted the EEG indicated an impression of "focal onset epilepsy" and "some frontal lobe dysfunction," and he recommended neuropsychological testing. *Id.* at 77.

Approximately two months later, Ms. Mager saw another pediatric neurologist, Dr. Koehn, who ordered another EEG—the results of which were normal. Pet'r's Ex. 6 at 22, ECF No. 8-7. Dr. Koehn noted, referring to the original abnormal EEG, that "[t]he 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." *Id.* at 20. Although the medication appeared to control her seizure activity, Ms. Mager's father and stepmother noted undesirable side effects of the medication and requested she be weaned off Depakote. *Id.* at 24. Accordingly, Dr. Koehn agreed to gradually wean Ms. Mager from Depakote and referred her for neuropsychological testing. *Id.* at 28; *see also* Pet. at 1.

Shortly after seeing Dr. Koehn, Ms. Mager saw another physician, Dr. Waltonen, for neuropsychological testing. Pet'r's Ex. 6 at 6. Dr. Waltonen observed she had "a history of some type of learning difficulty at least in the speech and language area." *Id.* He also noted Ms. Mager had a family history of epilepsy and seizures on her maternal side. *Id.* at 2. He noted reports of "increasing problems with doing well in school" and Ms. Mager's teachers indicated she had "problems following directions." *Id.* at 1, 4. Ultimately, Dr. Waltonen 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.

From April 2008 to October 2012, Ms. Mager did not experience any seizure activity and appeared to function normally. Her school records did not indicate any abnormalities. *See* Pet'r's Ex. 83, ECF No. 144-3. The results of sport physicals she received in August 2009 and March 2012 were normal. Pet'r's Ex. 10 at 15–17, ECF No. 9-3; Pet'r's Ex. 14 at 1–2, ECF No. 12-2. During a physical exam in January 2012, she reported she had not experienced seizure activity for four years. Pet'r's Ex. 10 at 18. Ms. Mager received her second HPV vaccination on 11 September 2012. Pet'r's Ex. 4 at 1, ECF No. 8-5. The following month, on 10 October 2012, she suffered a seizure and was taken to the emergency department of a nearby medical center. Pet'r's Ex. 7 at 9, ECF No. 8-8. Her evaluation, which included an [electrocardiogram], was normal. *Id.* at 13–14. She was diagnosed with a "[p]robable seizure" and discharged. *Id.* at 14.

In a visit with her primary care doctor the next month, she reported two additional seizures occurring on 19 October 2012 and 7 November 2012 after her ER visit. Pet'r's Ex. 9 at 39, ECF No. 9-2. Her doctor prescribed an anti[-]seizure

medication, Depakote, and referred her to a neurologist. *Id.*

Neurologist Dr. Edgar saw Ms. Mager a couple months later in January 2013. Pet'r's Ex. 9 at 24–25. According to Dr. Edgar's note, "[t]he 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. Edgar believed Ms. Mager suffered from primary generalized seizure disorder, and he noted the "age of onset at approximately 11 years of age suggests the possibility of juvenile myoclonic epilepsy, although no myoclonic seizures are reported." *Id.* at 31. He recommended Depakote, but due to Ms. Mager's objections, he directed her to begin weaning off Depakote and prescribed Keppra, an alternative anti[-]seizure medication, instead. *Id.* at 8.

Dr. Edgar observed during a follow-up appointment in July 2013 that Ms. Mager's compliance with her Keppra prescription was "less than ideal"; she had a sub-therapeutic level of the medication in her blood according to a test on 30 May 2013. Pet'r's Ex. 9 at 3. Ms. Mager wanted to stop using Keppra, but Dr. Edgar persuaded her to remain on the drug given her history of seizures. *Id.* at 4. Due to her age at the onset of her seizure condition, Dr. Edgar again noted "probable juvenile myoclonic epilepsy." *Id.*

Months later, on 11 January 2014, Ms. Mager was found unresponsive at a friend's house and was rushed to the emergency department of a nearby hospital where she was pronounced dead upon arrival. Pet'r's Ex. 8 at 2, ECF No. 8-9. The local police department reported a witness statement that Ms. Mager had been "missing a lot of doses of her medication," and her father reported that "she was having seizures more frequently." Pet'r's Ex. 13 at 2, ECF No. 9-6.

According to an autopsy, Ms. Mager suffered pulmonary edema and brain changes consistent with a seizure disorder. Pet'r's Ex. 16 at 10, ECF No. 18-2. There was subpial gliosis in sections of her brain. *Id.* at 16. A toxicology screen showed therapeutic levels of Keppra in her blood. Pet'r's Ex. 13 at 11. The cause of Ms. Mager's death was "seizure disorder" according to her death certificate. Pet'r's Ex. 1 at 1, ECF No. 8-2.

The parties agree Ms. Mager suffered from a seizure disorder that caused her death, [2021 Mot. for Review Oral Arg. Tr. at] 6:14–16[, ECF No. 197], but they dispute the underlying diagnosis. Pet'r's Prehr'g Br. at 9, ECF No. 168 ("Petitioner contends [Ms. Mager] suffered from autoimmune epilepsy that resulted in sudden unexpected death with epilepsy or SUDEP."); Gov't's Prehr'g Br. at 1, ECF No. 180 ("the evidence supports that Ms. Mager most likely suffered from juvenile myoclonic epilepsy").

Mager, 158 Fed. Cl. at 140–42.

II. The Petition and Procedural History Before the Special Master

The procedural history before the Special Master comes primarily from the Court's 2022 Opinion and Order granting petitioner's 2021 Motion for Review:

> Petitioner filed his petition alleging the HPV vaccination caused Ms. Mager to suffer a seizure disorder leading to her death on 11 January 2014. Pet. at 2. All relevant medical records were submitted, and the record was complete on 17 February 2015. *See* Statement of Completion, ECF No. 23. A couple months later, the Secretary filed his report contesting causation and arguing Ms. Mager's seizure disorder preexisted her vaccination. *See* Resp't's Rule 4(c) Report, ECF No. 25. After a change in counsel and experts, and multiple extensions of time, the parties submitted their experts' reports. *See* Pet'r's Ex. 55, ECF [No.]116-1; Gov't's Ex. Z, ECF No. 128-1; Gov't's Ex. AA, ECF No. 129-1; Pet'r's Ex. 85 [("Shafrir Reply Report")], ECF No. 165-2; Gov't's Ex. CC, ECF No. 182-1; Gov't's Ex. BB, ECF No. 183-1. Petitioner's expert, Dr. Shafrir, asserted Ms. Mager's epilepsy was autoimmune in nature based, in part, on autoimmune reactions to the vaccine. Pet'r's Ex. 55 at 18. Respondent's experts, Dr. Kohrman and Dr. Fujinami, however, both stated Ms. Mager suffered from juvenile myoclonic epilepsy ("JME"). Gov't's Ex. Y at 7, ECF No. 95-3; Gov't's Ex. CC at 1–2.
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> The Special Master ordered the parties to submit briefs in advance of potential adjudication on 20 November 2019, ECF No. 142. After multiple extensions, Mr. Mager filed a supplemental expert report from Dr. Shafrir on 25 July 2020, ECF No. 167, and his brief on 27 July 2020 . . . . The Secretary, again after multiple extensions, filed his supplemental expert reports from Dr. Fujinami and Dr. Kohrman, as well as his brief, on 10 February 2021, ECF Nos. 180–83. Mr. Mager filed his reply brief on 26 March 2021, ECF No. 186.
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> In the interim period between the parties' briefing and the Special Master's decision, a significant colloquy between the Special Master and petitioner took place. The Special Master issued an order in June asking petitioner to "identify the source of the diagnostic criteria for autoimmune epilepsy listed in his [prehearing] brief." Order at 1, ECF No. 187. Petitioner responded accordingly the next day but noted "[t]he criteria are discussed in that section *solely* to demonstrate that autoimmune epilepsy can present as milder epilepsy." Status Report Re Order of June 16, 2021 . . . at 1, ECF No. 188 (emphasis added).
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> The Special Master then issued his decision denying compensation the following month on 29 July 2021. *See* Decision Den. Compensation . . . . In his decision, the Special Master denied petitioner's claim on the basis that there was insufficient evidence to support a diagnosis of Autoimmune Epilepsy. *Id.* at 16–17.

Mager v. Sec'y of Health & Hum. Servs., 158 Fed. Cl. 136, 142–43 (2022).

On 27 August 2021, petitioner moved for review of the Special Master's Decision

Denying Compensation. *See* Mot. for Review ("2021 Mot. for Review"), ECF No. 191. Petitioner alleged the Special Master erred by analyzing the diagnostic criteria of autoimmune epilepsy as prerequisites to causation-in-fact. *Id.* at 16. Petitioner asserted his theory of causation did not hinge on the diagnostic criteria. *Id.* The Court granted petitioner's Motion for Review on 21 January 2022, finding the Special Master had not analyzed petitioner's theory of causation through the appropriate lens. *Mager*, 158 Fed. Cl. at 157. The Court vacated the 29 July 2021 Decision Denying Compensation and remanded the case to the Special Master to perform the causation analysis. *Id*. The Special Master held hearings and received briefs in March and April of 2022, heard oral arguments on 8 April 2022, and issued a ruling finding entitlement on 19 April 2022. Ruling Finding Entitlement at 1, 23. On 5 December 2022, the Special Master issued a decision awarding compensation, ECF No. 240. On 4 January 2023, respondent moved for review of the Ruling Finding Entitlement and filed a supporting memorandum. *See* Resp't's Mot. for Review, ECF No. 242; Resp't's Mem. in Supp. of Mot. for Review ("2023 Mot. for Review"), ECF No. 243. Petitioner filed a response to respondent's Motion for Review on 3 February 2023. *See* Pet'r's Resp. to Resp't's Mem. in Supp. of Mot. for Review ("Pet'r's Resp."), ECF No. 244. The Court heard oral argument on 4 April 2023. *See* 4 April 2023 Oral Arg. Tr. ("Tr.") at 1:18, ECF No. 247.

A. The Special Master's Ruling Finding Entitlement

In his Ruling Finding Entitlement, the Special Master summarized Ms. Mager's medical records and related findings of fact. *See* Ruling Finding Entitlement at 2–16. The Special Master found moot the issue of Ms. Mager's specific epilepsy diagnosis as the Court's remand found the distinction inapplicable to petitioner's theory of causation. *Id*. at 27–28. The Special Master analyzed petitioner's claim under *Loving* and additionally examined whether respondent provided preponderant evidence showing Ms. Mager's death resulted from the natural course of her underlying disorder rather than the vaccination. *Id*. at 28–55.

1. The Special Master's Factual Summary

Based on evidence regarding the course and timeline of her enuresis (bed-wetting) and tongue-biting episodes, the Special Master determined Ms. Mager's seizure disorder began prior to her 2 October 2007 HPV vaccination. *See id*. at 3–6. The Special Master found Dr. Kohrman's expert testimony persuasive: Dr. Kohrman presented evidence pharmacological interventions had not resolved Ms. Mager's enuresis until she started taking anti-seizure medications. *Id.* at 4–6. Respondent also proffered evidence of the relatively rare incidence of enuresis among Ms. Mager's age group. *Id*. at 4.

In examining evidence of tongue-biting prior to the first HPV vaccination, the Special Master relied on contemporaneous medical records of the 14 November 2007 seizure referring to a history of tongue-biting episodes. Ruling Finding Entitlement at 4–5. While the Special Master considered the lack of pre-2007 medical records mentioning tongue-biting, the Special Master credited the medical records because both parties' expert physicians testified to the commonality of retrospective symptom identification in seizure patients and petitioner himself agreed Ms. Mager experienced tongue-biting episodes prior to her 14 November 2007 seizure. *Id*. at 4–7. Additionally, the Special Master considered the testimony of petitioner's expert, Dr.

Shafrir, stating Ms. Mager "quite likely" had nocturnal seizures[2] during the month prior to the 14 November 2007 seizure. *Id*. at 5.

2. The Special Master's Summary of Procedural History

In reciting the case's procedural history, the Special Master restated several sections of expert witness reports related to petitioner's medical theory of causation under challenge-rechallenge. *Id*. at 17–21. Dr. Kohrman's report filed in response to Dr. Shafrir disputed the alleged occurrence of challenge-rechallenge. *Id*. at 20. The Special Master noted, "Dr. Kohrman did not address the medical theory that Dr. Shafrir had proposed to explain how a[n] HPV vaccine can aggravate a preexisting seizure disorder." Ruling Finding Entitlement at 20.

3. The Special Master's Analysis

While acknowledging the specific diagnosis of epilepsy was no longer in dispute, the Special Master first summarized the parties' arguments regarding the diagnosis of JME versus autoimmune epilepsy. *Id*. at 24–28. In his causation analysis, the Special Master addressed *Loving* prongs one, two, and three, then addressed proximate temporal relationship, prong six, before examining reputable medical theory, prong four, and logical sequence of events, prong five. *Id.* at 28–53. The Special Master reasoned his findings on proximate temporal relationship impacted the findings on reputable medical theory and logical sequence of events. *Id*. at 31.

In analyzing *Loving* prongs one and two, Ms. Mager's condition before and after vaccination, the Special Master found Ms. Mager had not experienced seizures or required seizure medications for the nearly five-year period preceding the 2012 HPV vaccination. *Id.* at 28. Dr. Kohrman argued Ms. Mager experienced unwitnessed seizures in her sleep during this period, but the Special Master found this contention unpersuasive against the Mager family's history of noting and reporting signs of seizures. *Id*. The Special Master noted the onset of Ms. Mager's seizure disorder prior to the 2007 HPV vaccination did not preclude petitioner's significant aggravation claim based on the 2012 HPV vaccination. Ruling Finding Entitlement at 29.

In deciding whether Ms. Mager's change in condition was a "significant aggravation" under *Loving* prong three, the Special Master acknowledged "[t]his issue is close." *Id*. at 29–31. The Special Master found persuasive petitioner's characterization of Ms. Mager's health in terms of her risk for SUDEP. *Id*. Petitioner asserted Ms. Mager's seizure-free status prior to the 2012 vaccination meant she was at very little risk, if any, for SUDEP. *Id.* at 30. The Special Master also considered petitioner's argument Ms. Mager's epilepsy became "uncontrolled" after the second vaccination. *Id*.

The Special Master noted merit in respondent's counterarguments on *Loving* prong three,

[2] Nocturnal seizures "can cause abnormal movement or behavior during sleep" and symptoms "may range from awakening for no clear reason, sometimes multiple times a night, to shouting, screaming and violent movements of the arms and legs." Johns Hopkins Medicine, *Nocturnal Seizures*, (last visited June 1, 2023) https://www.hopkinsmedicine.org/health/conditions-and-diseases/epilepsy/nocturnal-seizures.

acknowledging each of the three seizures occurring in the immediate aftermath of the 2012 vaccination "seem[ed] mild." *Id*. The Special Master further contemplated Ms. Mager's subsequent eight-month seizure-free—albeit medicated—period. Ruling Finding Entitlement at 30. The Special Master further considered respondent's argument Ms. Mager's epilepsy remained mild both before and after the 11 September 2012 HPV vaccination—an argument based in part on Dr. Shafrir's own testimony. *Id.* The Special Master nevertheless found Ms. Mager's change in condition—from being seizure-free and not needing medication to experiencing seizures and requiring medication—was a "significant aggravation" under *Loving* prong three. *Id*. at 30–31.

The Special Master found petitioner "persuasively" met his burden of proof on *Loving* prong six. *Id*. at 37. The Special Master noted the parties' agreement on the timeline of seizures: Ms. Mager experienced generalized tonic-clonic seizures[3] occurring 43 days after the 2007 vaccination and 29 days after the 2012 vaccination. *Id.* at 31–32. The Special Master's analysis centered on the contested definition of a "medically acceptable timeframe" for challenge-rechallenge under *Loving* prong six. *Id*. at 31–40. On this point, the Special Master considered evidence offered by Dr. Shafrir regarding the Slade post-marketing surveillance study, which utilized a "biologically plausible" interval for autoimmune reactions between four and 42 days after HPV vaccination. Ruling Finding Entitlement at 32–33 (citing Barbara A. Slade et al., *Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine*, Am. Med. Ass'n (2009)).

The Special Master specifically noted respondent's pre-hearing filings did not challenge the reasonableness of a 42-day (or 43-day) interval but rather argued temporal proximity was insufficient to establish causation. *Id.* at 33. Respondent's expert Dr. Fujinami nevertheless challenged Dr. Shafrir's proposed 42-day interval at the hearing. *Id*. at 34–35. The Special Master considered Dr. Fujinami's testimony, asserting the clinical manifestations of an autoimmune reaction to a vaccination would occur within 14 days. *Id.* The Special Master noted Dr. Fujinami based his testimony on personal knowledge of primate studies on the subject and personal observations made while experimenting with mice. *Id.* The Special Master observed Dr. Fujinami did not cite specific studies. *Id*. Dr. Fujinami further admitted some studies have allowed for autoimmune responses more than 40 days after vaccination. Ruling Finding Entitlement at 35. The Special Master also briefly referred to the existence of testimony from Dr. Kohrman on the issue of the timeline, however, the Special Master did not address how Dr. Kohrman's testimony on the timeline impacted his legal reasoning, if at all. *Id.*

In further analyzing the timeline under *Loving* prong six, the Special Master contemplated respondent's cross-examination of Dr. Shafrir regarding a study cited in Dr. Shafrir's report. *Id*. at 33 (citing Margaret Stanley, *HPV – Immune Response to Infection and Vaccination*, 5 INFECTIOUS AGENTS & CANCER 19 (2010)). The study in question suggested memory B cells on rechallenge from HPV vaccination produce peak antibody levels within three to five days. *Id*. The Special Master remarked Dr. Shafrir could not persuasively account for why Ms. Mager's seizures started more than three weeks after peak antibody levels and fell back

[3] Generalized tonic-clonic seizures, or grand mal seizures, affect both sides of the brain and can make a person cry out, lose consciousness, fall to the ground, and have muscle jerks or spasms. CDC, *Types of Seizures*, (last visited June 1, 2023) https://www.cdc.gov/epilepsy/about/types-of-seizures.htm.

on the Slade study. *Id*.

The Special Master did not credit Dr. Fujinami's opinions on the timing of clinical manifestations. *Id*. at 38–39. The Special Master listed three distinct reasons: (1) counter to typical Vaccine Program practice, neither respondent nor Dr. Fujinami disclosed said opinions in pre-hearing filings and reports; (2) the opinion was inconsistent with other evidence such as the Slade post-marketing study; and (3) Dr. Fujinami did not present literature supporting his opinions. Ruling Finding Entitlement at 38–39.

The Special Master found petitioner advanced a medically acceptable timeframe supported by relevant literature and expert testimony, and the alleged significant aggravation occurred within said timeframe. *Id.* at 37–38. While noting the Slade study alone was sufficient to credit Dr. Shafrir's opinion on timing, the Special Master cited additional support from the Vaccine Injury Table, wherein Guillain-Barre Syndrome ("GBS") induced by the influenza vaccine had been accepted within a three to 42-day interval. *Id.* Addressing the timeframe of the alleged 2007 challenge event, the Special Master stated, "[w]hether 43 days after the first HPV vaccination is an appropriate temporal interval is less important because Mr. Mager's claim is not based on the first HPV vaccination." *Id*. at 37 n.24. The Special Master also cited language from the Federal Circuit cautioning against special masters setting "hard and fast deadlines." *Id*. at 38 (quoting *Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1383–84 (Fed. Cir. 2015)).

The Special Master held, as a matter of law, preponderant evidence of a challenge-rechallenge occurrence meets the definition of "a medical theory causally connecting the vaccination and the injury" under *Althen* prong one (*Loving* prong four). *Id*. at 47–48 (quoting *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005)). The Special Master cited *Capizzano* and *James-Cornelius* as support for using evidence of a challenge-rechallenge occurrence to satisfy the *Loving* prong four definition of a reliable medical theory. Ruling Finding Entitlement at 47–48 (citing *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317 (Fed. Cir. 2006); *James-Cornelius v. Sec'y of Health & Hum. Servs.*, 984 F.3d 1374, 1381 (Fed. Cir. 2021)) ("[I]n 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.'"). The Special Master compared *Loving* prong five to "asking whether the vaccine did cause the injury" and thus reasoned "[e]vidence that a vaccine did cause an injury must imply that the vaccine can cause the injury." *Id.* at 48.

The Special Master determined petitioner met his burden on *Loving* prong four because a challenge-rechallenge occurrence can cause the alleged injury. *See id.* at 48–49. In support, the Special Master cited the following four evidentiary points advanced by petitioner: (1) World Health Organization literature defining "the relationship between challenge-rechallenge as an adverse reaction to a vaccine as one of *certain causality*," *id*. at 42 (citing Pet'r's Ex. 57 at 4, ECF No. 116-3); (2) evidence of increased incidence of epilepsy among individuals with systemic lupus erythematosus, suggesting epilepsy may sometimes have an autoimmune component, *id*. (citing Antonio Greco et al., *Autoimmune Epilepsy*, 15 Autoimmunity Revs. 221 (2016)); (3) a study showing 9–14% of epilepsy patients have detectable bloodstream levels of

autoimmune antibodies, *id*. (citing Jehan Suleiman et al., *Autoantibodies to Neuronal Antigens in Children with New-Onset Seizures*, 54 Epilepsia 2091 (2013)); and (4) evidence from the Slade post-marketing study reporting "convulsions" made up "8.8% of the serious reported side effects on VAERS reports from June 2001 through December 2008," Ruling Finding Entitlement at 42 (citing Slade, *supra*).

The Special Master considered contrary arguments from Dr. Fujinami, who advanced studies reviewed by the World Health Organization detecting no increases in autoimmune diseases or seizures among HPV vaccinees. *Id.* at 45. Dr. Fujinami inferred "if the HPV vaccination could cause a dysregulated immune response, some evidence . . . would have shown up in these large studies." *Id*. The Special Master took note of Dr. Fujinami's explanation of challenge-rechallenge: "Dr. Fujinami explained how repeat vaccinations can enhance the immune response. However, the challenge-rechallenge paradigm requires appropriate timing. In this case, [Dr. Fujinami opined Ms. Mager]'s seizures occurred too long after the vaccinations to be caused by the vaccinations." *Id*. (internal citations omitted). The Special Master disagreed, positing the basic chronology of Ms. Mager's clinical course fit the framework of challenge-rechallenge. *Id*. at 48.

The Special Master also considered petitioner's argument distinguishing a burden to provide a "medical theory" from a requirement to provide a "biologic mechanism." *Id*. at 45–46. Petitioner asserted establishing challenge-rechallenge fulfilled the requirements of a medical theory. Ruling Finding Entitlement at 46. The Special Master noted respondent "did not address" petitioner's distinction between medical theory and biologic mechanism. *Id.* at 46 n.29. Petitioner also advanced alternate theories of causation apart from challenge-rechallenge, including molecular mimicry; the Special Master found these theories unpersuasive. *See id.* at 49–50.

The Special Master found petitioner carried his burden for *Loving* prong five by showing an appropriate sequence of events to prove challenge-rechallenge. *Id*. at 52. The Special Master centered his analysis around the parties' arguments regarding indicators of chronic neuroinflammation. *Id*. at 51. The Special Master noted the following opinions proffered by the parties' expert witnesses: (1) Dr. Shafrir's opinion the subpial gliosis found on autopsy proved chronic neuroinflammation; (2) Dr. Fujinami's and Dr. Kohrman's assertions seizures alone can account for the gliosis; (3) Dr. Kohrman's argument Ms. Mager's MRI taken after her 14 November 2007 seizure showed no indications of inflammation; (4) Dr. Kohrman's argument Ms. Mager's May 2012 lab results showed normal levels of white blood cells in her bloodstream; and (5) Dr. Fujinami's opinion Ms. Mager's seizures resulted from poor medication compliance. *Id*. at 51–52.

Although the Special Master did not delineate which arguments were persuasive, he concluded petitioner fulfilled the requirements of *Loving* prong five by referring to the basic chronology of Ms. Mager's clinical course discussed for *Loving* prong four. Ruling Finding Entitlement at 48–49, 52. The Special Master stated, "there is no dispute that challenge-rechallenge can show that a vaccine harmed a person and then, on re-exposure, harmed the person again. . . . Mr. Mager has shown this sequence of events for [Ms. Mager]." *Id.* at 52 (internal citation omitted). The Special Master also addressed the telephone statements

of treating physician Dr. Koehn in July 2008 opining the HPV vaccine did not cause Ms. Mager's seizures. *Id.* at 52–53. The Special Master found Dr. Koehn's statements were based on "incomplete information" as they occurred before the 2012 rechallenge event. *Id*.

After finding petitioner met his *prima facie* case, the Special Master found respondent failed to provide sufficient evidence showing the 2012 vaccination was not a significant factor in Ms. Mager's death. *Id*. at 53–55. On this point, respondent's arguments included the assertion Ms. Mager suffered from JME and a secondary argument her death was due to the natural course of her epilepsy. *Id.* at 53. Respondent based the JME assertion on Dr. Kohrman's testimony showing a person with JME not taking anti-seizure medications may experience years without seizures before a sudden relapse. Ruling Finding Entitlement at 53. The Special Master found this argument had a good-faith basis but was "outweighed by the value of challenge-rechallenge." *Id.*

The Special Master contemplated respondent's secondary argument, which asserted Ms. Mager's death resulted from the following underlying factors: (1) patients with epilepsy who are not taking medications redevelop seizures unpredictably; (2) Ms. Mager was reluctant to take Depakote and had mixed compliance with Keppra; and (3) Dr. Shafrir stated Ms. Mager's SUDEP was "not correlated to the vaccine." *Id*. at 54. Petitioner responded by citing Dr. Kohrman's characterization of Ms. Mager's epilepsy as "uncontrolled" before her death. *Id*. The Special Master noted this argument did not prove the lack of control resulted from the 2012 vaccination. *Id*. The Special Master also considered petitioner's clarification of Dr. Shafrir's testimony: although Dr. Shafrir stated Ms. Mager's SUDEP was not correlated with the vaccine, Dr. Shafrir did correlate Ms. Mager's death with her epilepsy, which in turn related to the vaccine. *Id*.

In his holding, the Special Master acknowledged "[t]his issue, too, is close." Ruling Finding Entitlement at 55. The Special Master pointed out respondent's lack of evidence regarding the general incidence of SUDEP among persons with mild epilepsy. *Id.* Absent such evidence, the Special Master found although respondent's claim "seem[ed] possible," respondent had "not established this argument by a preponderance of the evidence." *Id*.

Based on these findings, the Special Master concluded petitioner carried his burden of proof for an off-Table significant aggravation claim related to Ms. Mager's 11 September 2012 HPV vaccination. *Id.* The Special Master issued the Ruling Finding Entitlement on 19 April 2022 and the Decision Awarding Compensation on 5 December 2022.

III. Respondent's Motion for Review and Petitioner's Arguments

On 4 January 2023, respondent moved for review of the Special Master's Ruling Finding Entitlement of 19 April 2022. 2023 Mot. for Review at 1. Respondent asserts "the Special Master erroneously found that Ms. Mager's waking seizure on November 14, 2007 evidenced a significant aggravation of her preexisting epilepsy, that the evidence established a medically reasonable timeframe to infer vaccine causation, and that the challenge-rechallenge paradigm satisfied petitioner's burden under *Althen* prong 1 and *Loving* prong 4." *Id.* at 2. The Court summarizes the parties' arguments for each objection in turn.

A. The Finding Ms. Mager's 14 November 2007 Seizure Evidenced a Significant Aggravation of her Pre-Existing Epilepsy, and Established a Challenge Event

Regarding the first HPV vaccination, respondent submits the "Special Master erred as a matter of law by finding Mr. Mager's claim was not based on the first HPV vaccination, erroneously failed to create a sufficient record to permit review as required by [VRCFC] 3(b)(2), and arbitrarily and capriciously found that Ms. Mager's November 14, 2007 seizure evidenced a significant aggravation of her pre-existing epilepsy and requisite challenge event." *Id.* at 11. Respondent argues the Special Master "applied the wrong legal standard by erroneously determining that 'Mr. Mager's claim is not based upon the first HPV vaccination.'" *Id.* at 7 (quoting Ruling Finding Entitlement at 37 n.24). Respondent contends "because the claim is based on challenge-rechallenge, Ms. Mager's first vaccination was, in fact, critical to petitioner's causation theory." *Id.* Respondent, citing *Nussman v. Secretary of Health and Human Services*, explains petitioner is required to establish the first HPV vaccination as a challenge event and "failure to preponderantly establish a challenge event is fatal to a claim based on a challenge-rechallenge paradigm." *Id.* at 8 (citing 83 Fed. Cl. 111, 120 (2008) (Sweeney, J.) ("There can only be a rechallenge if there was an initial challenge and associated adverse reaction.")). Respondent argues the Special Master erroneously deemphasized the events surrounding the first HPV vaccination and "failed to analyze in the first instance how Ms. Mager's November 14, 2007 waking seizure meets the statutory definition of a 'significant aggravation.'" 2023 Mot. for Review at 8. Respondent discusses the Special Master's failure to address the arguments made in respondent's briefing, specifically the argument asserting the 14 November 2007 seizure was not a significant aggravation of the epilepsy. *Id.* Respondent argues petitioner is required to establish a challenge event to rely on the challenge-rechallenge paradigm and has not done so here. *Id.* at 7–9 (citing *Nussman*, 83 Fed. Cl. at 120). Respondent asserts there is no evidence supporting the presumption the 2007 waking seizures were different from nocturnal seizures in severity. *Id.* at 9–10. Respondent consequently argues there is no evidence to support the first HPV vaccination was a challenge event, i.e., Ms. Mager's seizures were worse after the first HPV dose. *Id.* Even if there was a challenge event, respondent argues, the symptoms following "nearly five years without any seizure activity[] do[] not evidence 'a substantial deterioration' in Ms. Mager's health." *Id.* at 11 (quoting 42 U.S.C. § 300aa-33(4)).

Petitioner claims respondent "mischaracterizes the Special Master's assertion as irrelevant," but "the Special Master is merely stating that [p]etitioner is not claiming an independent injury from the first dose of HPV vaccination." Pet'r's Resp. at 14. Petitioner asserts respondent's arguments "confuse[] petitioner's claim of significant aggravation with the theory of causation, which is challenge-rechallenge." *Id.* Petitioner explains a significant aggravation claim can be solely based on the second HPV dose, but the first vaccination is critical to the theory of causation. *Id.* at 14–15. Petitioner defends the Special Master's factual analysis by pointing to: (1) the discussion of facts; (2) Ms. Mager's health prior to and after the first vaccination; and (3) expert testimony. *Id.* at 15. Regarding the severity of the seizures, petitioner avers the record demonstrated significant aggravation following the first dose of the HPV vaccination. *Id.* at 16.

B. The Finding Timing Supports Petitioner's Theory of Challenge-Rechallenge

Respondent argues the determination "the timing here supports a finding that Ms. Mager experienced a challenge event following her October 2, 2007 vaccination is also deeply flawed." 2023 Mot. for Review at 12. Respondent asserts the Slade article, which the Special Master relied upon for a "window of plausibility," is not "related to the alleged injury in this case." *Id.* Additionally, respondent argues petitioner's expert "had no opinion as to what made [four] to 42 days 'biologically plausible.'" *Id.* Respondent also criticizes the Special Master's citation of the Vaccine Injury Table as support for the timing. *Id.* at 12–13. Respondent acknowledges the Vaccine Injury Table may be helpful but argues "the Special Master did not explain how the Table timeline for onset of GBS following influenza vaccination is relevant to the development of waking seizures following an HPV vaccination." *Id.* at 13. Respondent contends the Special Master did not "provide[] a rational basis for selecting a timeframe generally ascribed to the development of a peripheral demyelinating condition—GBS—as opposed to some other timeframe contained in the Vaccine Injury Table." *Id.* at 14. Respondent specifically disagrees with the timing of the second HPV dose supporting a rechallenge event. 2023 Mot. for Review at 14–15. Respondent argues the review articles relied upon by petitioner's expert were contrary to the facts, and the Special Master erred in giving the articles credence. *Id.* at 15. Respondent contends in a footnote the "Special Master further erred in rejecting the testimony of respondent's expert immunologist, Dr. Fujinami, as to timing." *Id.* at 15 n.4.

In defending the Slade article, petitioner explains "GBS is, in fact, an autoimmune disease" and a GBS comparison is therefore applicable as evidence of the timing being "biologically plausible." Pet'r's Resp. at 17. Petitioner asserts while the Vaccine Injury Table is "not dispositive," it "can be properly relied upon" as the Special Master did after citing cases using the Vaccine Injury Table as support for timing. *Id.* at 18. Petitioner contends the Special Master's decision on choosing the GBS-flu vaccine temporal window was not arbitrary and capricious because "it was based on expert testimony and scientific studies" and provides "additional[] though unnecessary support." *Id.* at 18–19. Petitioner argues the Special Master was allowed to extend the support timeline by one day because the Federal Circuit "has admonished special masters not to set 'hard and fast deadlines.'" *Id.* at 19 (quoting *Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1383–84 (Fed. Cir. 2015)). Petitioner rebuts respondent's implications the Special Master "failed to consider Dr. Fujinami's testimony" and states the Special Master correctly observed neither of respondent's experts "addressed timing in their original or supplemental reports" or rebutted the timing proposed by petitioner. *Id.* at 19–20.

C. The Finding Challenge-Rechallenge Paradigm Satisfied *Loving* Prong Four

Respondent asserts the Special Master "erred in finding challenge-rechallenge, by itself, satisfied petitioner's burden to show preponderant evidence of a reliable medical theory under *Loving* prong 4 or *Althen* prong 1." 2023 Mot. for Review at 16. Citing *Capizzano*, respondent argues the challenge-rechallenge paradigm is "generally proffered in the context of *Althen* prong 2[(*Loving* prong five)]." *Id.* (citing *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317 (Fed. Cir. 2006)). Respondent contends the Federal Circuit "did not find challenge-rechallenge sufficient by itself to satisfy *Althen* prong 1[(*Loving* prong four)]." *Id.* Respondent asserts petitioner's theory of challenge-rechallenge does not meet "petitioner's burden to provide a

reliable medical or scientific explanation of how the vaccine can bring about the injury." *Id.* at 17–18. Referring to the error in timing, respondent asserts "in order to assess whether a proposed time relationship is plausible, one must have some understanding of how the vaccine is thought to bring about the injury—that is, the proposed causal mechanism." *Id.* at 18. Respondent argues petitioner's expert did not "describe any pathology for how an HPV vaccine can significantly aggravate a seizure disorder" or a plausible timeframe, and therefore relying on the challenge-rechallenge paradigm as a reliable theory under *Althen* prong one or *Loving* prong four is erroneous. *Id.* at 18–19.

Petitioner asserts the theory of causation is the challenge-rechallenge paradigm. Pet'r's Resp. at 20. Petitioner emphasizes the Special Master reviewed the evidence and found petitioner met the burden to present a plausible theory. *Id.* Petitioner defends the Special Master's use of *Capizzano* "as a starting point" and points out "the [Federal] Circuit in its *de novo* review accept[ed] the [s]pecial [m]aster's finding of [p]rong 1 noting that 'In so deciding, the chief special master relied on evidence of 'rechallenge.'" *Id.* at 21 (citing *Capizzano*, 440 F.3d at 1322). Petitioner further notes the Federal Circuit in *Capizzano* allowed evidence from one prong to satisfy another prong, so the evidence proffered here for *Loving* prongs five and six may also support prong four. *Id.* at 21–22 (quoting *Capizzano*, 440 F.3d at 1326 ("We see no reason why evidence used to satisfy one of the *Althen* . . . prongs cannot overlap to satisfy another prong.")). Petitioner also argues the Federal Circuit does not "require identification and proof of specific biological mechanisms." *Id.* at 22 (quoting *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994)).

D. Burden to Establish Ms. Mager's Death Was the Natural Result of Her Epilepsy

Respondent argues "the Special Master erroneously shifted the burden to respondent to disprove that Ms. Mager's September 11, 2012 HPV vaccination caused her death." 2023 Mot. for Review at 19. Respondent, referencing petitioner's expert, asserts Ms. Mager's death was a result of SUDEP and not correlated to the vaccination. *Id.* at 19–20. Respondent argues because petitioner's expert "disavowed any relationship between Ms. Mager's vaccinations and her SUDEP, and given the Special Master's finding that the HPV vaccine did not cause Ms. Mager's epilepsy, the Special Master erred in shifting the burden to respondent to establish that Ms. Mager's death was the natural result of her epilepsy and finding respondent failed to meet the burden." *Id.* at 20.

Petitioner, citing *Walther*, explains "the burden shifts to [respondent] under the 'factor unrelated' inquiry to show that the pre-existing condition caused the significantly worsened condition." Pet'r's Resp. at 23 (citing *Walther v. Sec'y of Health & Hum. Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007)). Petitioner maintains he met the burden of proof, and therefore the burden shifts "to [r]espondent to prove an alternative cause, e.g. the natural course of [Ms. Mager's] disease, for either her epilepsy post the second vaccination or her subsequent death." *Id.* Petitioner asserts the Special Master "discussed the evidence related to [Ms. Mager's] death specifically and found the [r]espondent failed to meet [its] burden" and therefore did not err. *Id.* at 24 (citing Ruling Finding Entitlement at 55).

IV. Legal Standards

A. The Court's Review of a Special Master's Decision

The Vaccine Act provides this court jurisdiction to review a special master's decision upon timely motion of either party. *See* 42 U.S.C. § 300aa-12(e)(1)–(2). In reviewing the record of the proceedings before the Special Master, the Court may: (1) "uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision"; (2) "set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law"; or (3) "remand the petition to the special master for further action in accordance with the court's direction." § 300aa-12(e)(2). "Fact findings are reviewed . . . under the arbitrary and capricious standard; legal questions under the 'not in accordance with law' standard; and discretionary rulings under the abuse of discretion standard." *Saunders v. Sec'y of Dep't of Health & Hum. Servs.*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) (quoting *Munn v. Sec'y of Dep't of Health & Hum. Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992)).

It is not the Court's role "to reweigh the factual evidence, or to assess whether the special master correctly evaluated the evidence." *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (quoting *Munn*, 970 F.2d at 871). The Court also does "not examine the probative value of the evidence or the credibility of the witnesses. These are all matters within the purview of the fact finder." *Id.* (quoting *Munn*, 970 F.2d at 871). "Reversal is appropriate only when the special master's decision is arbitrary, capricious, an abuse of discretion, or not in accordance with the law." *Snyder ex rel. Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 718 (2009) (footnote omitted). The arbitrary and capricious standard "is a highly deferential standard of review[:] [i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines ex rel. Sevier v. Sec'y of Dep't of Health & Hum. Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991).

B. Causation in Vaccine Cases

"A petitioner seeking compensation under the Vaccine Act must prove by a preponderance of the evidence that the injury or death at issue was caused by a vaccine." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1341 (Fed. Cir. 2010) (citing 42 U.S.C. §§ 300aa-11(c)(1), -13(a)(1)). "A petitioner can show causation under the Vaccine Act in one of two ways": (1) "by showing that she sustained an injury in association with a vaccine listed in the Vaccine Injury Table[;] . . . [i]n such a case, causation is presumed"; or (2) "if the complained-of injury is not listed in the Vaccine Injury Table . . . the petitioner may seek compensation by proving causation in fact." *Id.* at 1341–42 (internal citation omitted). Vaccine cases employ a burden shifting standard: "[o]nce the petitioner has demonstrated causation, she is entitled to compensation unless the government can show by a preponderance of the evidence that the injury is due to factors unrelated to the vaccine." *Id.* at 1342 (citing *Doe v. Sec'y of Health & Hum. Servs.*, 601 F.3d 1349, 1351 (Fed. Cir. 2010); 42 U.S.C. § 300aa-13(a)(1)(B)).

"For off-table claims"—for a vaccine not included in the Vaccine Injury Table under 42 U.S.C. § 300aa-11(c)(1)(C)(i)—"that an injury was *either* 'sustained, or [] significantly aggravated,' a petitioner must show the vaccine 'caused' the injury or aggravation." *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa-11(c)(1)(C)(ii)). "A petitioner must prove by preponderant evidence that the vaccination caused significant aggravation by showing:"

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) . . . a proximate temporal relationship between the vaccination and the significant aggravation.

Id. (citing *Loving ex rel. Loving v. Sec'y of Dep't of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2009)). The Federal Circuit in *W.C.* espoused "[t]he *Loving* test combines the first three *Whitecotton* factors, which establish significant aggravation, with the *Althen* factors, which establish causation." *Id.* Accordingly, the standards for assessing *Althen* prongs one, two, and three also apply to *Loving* prongs four, five, and six. *Id.*

Under the first prong of *Althen*, "[a] petitioner must provide a 'reputable medical or scientific explanation' for its theory." *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Moberly ex rel. Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)). "While it does not require medical or scientific certainty, [the explanation] must still be 'sound and reliable.'" *Id.* (quoting *Knudsen ex rel. Knudsen v. Sec'y of Dep't of Health & Hum. Servs.*, 35 F.3d 543, 548–49 (Fed. Cir. 1994)). Petitioners "need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act." *Andreu ex rel. Andreu v. Sec'y of Dep't of Health & Hum. Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009). Where such evidence is introduced, it must not be viewed "through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. For satisfying the second *Althen* prong, "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (quoting *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005)). Lastly, "the proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

V. Whether the Challenge-Rechallenge Paradigm Can Establish Causation

Central to the parties' argument is the challenge-rechallenge paradigm. The parties

dispute: (1) whether the challenge-rechallenge paradigm can be used as a "reliable medical theory" as *Loving* prong four requires; (2) the standard for establishing a challenge event as part of a logical sequence of cause-and-effect under *Loving* prong five; and (3) what is important in establishing a challenge event. As the parties argue about the legal standards the Special Master applied, the Court reviews *de novo*. *See Saunders v. Sec'y of Dep't of Health & Hum. Servs.*, 25 F.3d 1031, 1033 (Fed. Cir. 1994). The Court first determines if the challenge-rechallenge paradigm can be used as a "reliable medical theory." Next, the Court determines what legal standard is applied to establish the challenge event in the challenge-rechallenge paradigm. Finally, the Court reviews caselaw from the Federal Circuit and the Court of Federal Claims where challenge-rechallenge was used in the causation-in-fact analysis.

A. Whether the Challenge-Rechallenge Paradigm Can Be Used as a "Reliable Medical Theory"

At oral argument, respondent attempted to distinguish *Capizzano*. Respondent first argued "*Capizzano* is not particularly . . . persuasive or doesn't speak to the issues in this case is [sic] that contrary to the Federal Circuit's finding, the chief special master did not analyze *Althen* prong three in the lower court." Tr. at 10:1–5. Respondent also asserted *Capizzano* is not persuasive because the underlying theory supporting the challenge-rechallenge paradigm has been discredited by other studies cited. Tr. at 21:6–14 ("[RESPONDENT]: . . . *Capizzano* is ultimately not persuasive . . . because the fundamental basis for the chief special master's decision that challenge-rechallenge was proof of causation was its very heavy reliance on the position of the Institute of Medicine. And the Institute of Medicine's position, at that time, was . . . evidence of challenge-rechallenge was tantamount to proving causation. And that has evolved."), 21:22–22:3 ("[RESPONDENT]: . . . [T]he Pollard and Selby study . . . was a particular case report . . . the Institute of Medicine had found that challenge/rechallenge was sufficient proof of causation that the tetanus vaccine can cause [GBS]. And that's changed. For all the reasons that are outlined in the Issac study . . . ."). Petitioner argued challenge-rechallenge might not be accepted in the context of GBS and tetanus, but "challenge-rechallenge is commonly accepted in the medical community as evidence of causation." Tr. at 25:5–7. Further, while the Institute of Medicine ("IOM") requires scientific certainty, petitioner asserts scientific certainty is a higher causality burden than the causality standard required by the Vaccine Act, and therefore an IOM position is acceptable to use in the vaccine injury context. Tr. at 35:22–36:4.

Additionally, respondent argued challenge-rechallenge is "only anecdotal evidence of causation" and a causal mechanism is required for a "reliable medical theory." Tr. at 28:15–29:1 ("[PETITIONER]: [The Institute of Medicine] still look[s] at rechallenge as a strong causal relationship. [RESPONDENT]: I disagree. . . . [The 2012 IOM] describes [challenge-rechallenge] as one attribute in the evaluation of clinical evidence. But it's treated very much like case reports . . . essentially anecdotal evidence."). Further, respondent suggested challenge-rechallenge cannot be used without something more; there needs to a mechanism for *Althen* prong three. Tr. at 30:8–13 ("[RESPONDENT]: [I]t's not just a theory has to be plausible or reliable in the abstract. To satisfy [*Althen*] prong one, [the theory] has to have some relationship to the case. . . . You can't really make that assessment without something additional that would inform whether or not the onset is medically reasonable . . . ."), 29:11–30:1 ("THE

COURT: So then [respondent]'s argument is that there must be an underlying mechanism to satisfy reliable medical theory? [RESPONDENT]: That's what I think would be the most useful. I would say that there has to be something more. . . . THE COURT: . . . What's the something more? [RESPONDENT]: . . . I would say some information about the underlying mechanism to explain whether or not the onset of the condition is medically reasonable."). Petitioner asserted "rechallenge was such a strong proof of causality that you needn't do anything else" and no underlying mechanism was required under Federal Circuit precedent. Tr. at 15:24–16:1.

A "challenge-rechallenge" circumstance exists when a person has a reaction to one administration of a vaccine or drug and then suffers the same or worsening symptoms after an additional administration of the same vaccine or drug. The Federal Circuit recognizes the challenge-rechallenge paradigm as the basis for causation. In *Capizzano*, the chief special master stated, "evidence of rechallenge constituted such strong proof of causality that it is unnecessary to determine the mechanism of cause—it is understood to be occurring." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1322 (Fed. Cir. 2006) (internal quotations and citations omitted). The Federal Circuit reaffirmed the notion in *James-Cornelius ex rel. E.J.*: "the occurrence of a challenge-rechallenge event . . . has been recognized as a basis for establishing causation." *James-Cornelius ex rel. E.J. v. Sec'y of Health & Hum. Servs.*, 984 F.3d 1374, 1381 (Fed. Cir. 2021) (citing *Capizzano*, 440 F.3d at 1322).

The procedural history of *Capizzano* is unique. At the time the special master decided *Capizzano*, the Court of Federal Claims recently issued *Althen v. Secretary of Health and Human Services*, which rejected the existing *Stevens* standard. *Capizzano v. Sec'y of Dep't of Health & Hum. Servs.*, No. 00-759V, 2004 WL 1399178, at *2 (Fed. Cl. June 8, 2004), *determination sustained,* 63 Fed. Cl. 227 (2004), *vacated and remanded sub nom. Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317 (Fed. Cir. 2006). Recognizing *Althen* could affect the causation analysis, the chief special master in *Capizzano* ordered the parties file supplemental briefing applying this court's legal analysis in *Althen* to the case. *Id.* While respondent is correct the procedural history of *Capizzano* is unique, the chief special master's foresight in having the parties provide supplemental briefing under the now controlling causation-in-fact *Althen* standard makes *Capizzano* applicable.

The issue in *Capizzano* at the Federal Circuit involved the special master's requirement of one of four types of evidence, which included challenge-rechallenge evidence, to demonstrate the logical sequence of cause and effect and whether the requirement was inconsistent with *Althen*. *Capizzano*, 440 F.3d at 1322. The Federal Circuit held the special master could not require specific types of evidence, but the use of circumstantial evidence was "envisioned by the preponderance standard." *Id.* at 1325 (quoting *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005)). Respondent argues because the petitioner in *Capizzano* did not proffer challenge-rechallenge, the theory was not properly analyzed; petitioner argues the distinction does not negate the use of the challenge-rechallenge paradigm as a "reliable medical theory." Tr. at 79:4–11 (respondent), 86:9–17 (petitioner). In *Capizzano*, the parties presented evidence on rechallenge through experts, and the special master found the rechallenge evidence persuasive to show a reliable medical theory. *See Capizzano*, 2004 WL 1399178 *13–16 (finding medical literature and experts persuasive for showing rechallenge can occur). At oral

argument, respondent admitted "the chief special master found [testimony] satisfied [*Althen*] prong one" in *Capizzano*. Tr. at 82:16–83:22. Indeed, the Federal Circuit acknowledged the special master "relied on evidence of 'rechallenge' in other injectees. . . . [which] constituted 'such strong proof of causality that it is unnecessary to determine the mechanism of cause—it is understood to be occurring.'" *Capizzano*, 440 F.3d at 1322 (quoting *Capizzano*, 2004 WL 1399178 *16). The Federal Circuit did not find error in the use of the challenge-rechallenge paradigm as a reliable medical theory or for the proximate temporal relationship between the vaccination and injury. *Id.* at 1325 ("There is no dispute that the first and third prongs of *Althen* . . . were satisfied.").

To further support *Capizzano* allowing for use of the challenge-rechallenge paradigm, the Federal Circuit in *James-Cornelius* recognized the use of rechallenge as a form of evidence for causation. *James-Cornelius*, 984 F.3d at 1380 (citing *Capizzano*, 440 F.3d at 1322). The parties disagree on whether *James-Cornelius* clarifies the use of challenge-rechallenge. *See* Tr. at 7:23–8:4 (respondent arguing *James-Cornelius* is dicta), 17:11–16 ("[PETITIONER]: . . . [*James-Cornelius*] reiterate[s] again that a challenge/rechallenge event has been recognized as a basis for establishing causation . . . because it's a lower standard, it doesn't mean that rechallenge is not . . . a reliable model for causation."). Respondent argues because the issue in *James-Cornelius* was about the reasonable basis standard for attorneys' fees, *James-Cornelius* is dicta regarding challenge/rechallenge. Tr. at 7:23–8:4. In *James-Cornelius*, the Federal Circuit addressed whether there was a reasonable basis for a vaccine claim. 984 F.3d at 1379. The Federal Circuit reviewed the evidence upon which the petitioner based the claim and found the evidence, including rechallenge evidence, supported a reasonable basis. *Id.* at 1379–80. The Federal Circuit expressly acknowledged "'rechallenge,' which has been recognized as a form of causation evidence," is acceptable evidence. *Id.* at 1380. Despite reasonable basis being a lower standard than preponderant evidence, the Federal Circuit's decision provides rechallenge evidence can be used as a form of causation evidence. *Id. James-Cornelius* affirms *Capizzano*'s allowance of the challenge-rechallenge paradigm for the causation-in-fact analysis. *Id.*; *Capizzano*, 440 F.3d at 1322.

Respondent's argument challenge-rechallenge "will never be sufficient in and of itself without some explanation" is contrary to Federal Circuit precedent. Tr. at 8:12–18, 29:11–30:1 ("[RESPONDENT]: . . . [T]here has to be something more. . . . some information about the underlying mechanism to explain whether or not the onset of the condition is medically reasonable."). Respondent, referencing *Althen*, explains challenge-rechallenge "is fundamentally a temporal association. And it's well established in the law that a temporal association, in and of itself, cannot establish causation." Tr. at 8:8–18. Respondent misunderstands *Althen*. In *Althen*, immediately prior to setting out the standard for causation-in-fact, the Federal Circuit stated: "Although probative, neither a *mere showing of a proximate temporal relationship* between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005) (emphasis added). "[A] mere showing of a proximate temporal relationship" is different than proffering a medically acceptable theory relying on timing. *Id.* A petitioner alleging causation because the injury was close to the vaccination is not sufficient. A petitioner alleging causation because the injury was close to multiple instances of the vaccination and within the timeframe of when the medically acceptable

theory expects to see the repeat injury may be sufficient. *Id.*

The Federal Circuit has explained "the *Althen* prongs 'must cumulatively show that the vaccination was a "but-for cause" of the harm.'" *Rickett v. Sec'y of Health & Hum. Servs.*, 468 F. App'x 952, 957 (Fed. Cir. 2011) (citing *Pafford ex rel. Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006)). The Court, during oral argument, used a hypothetical to explore this point. *See* Tr. at 32:5–35:21. A person receiving the flu shot for the first time gets numbness in his arm five days later. *Id.* A numb arm close to vaccine administration is not sufficient to show causation. *See Althen*, 418 F.3d at 1278. The same person receives the flu shot the next year and again gets arm numbness five days later. Tr. at 32:5–35:21. Every year the person receives the flu shot, they have arm numbness until finally their arm becomes completely paralyzed after the tenth annual shot. Tr. at 32:5–35:21. Challenge-rechallenge expects to see repetitive adverse reactions after the administration of a vaccine within a certain timeframe. *Althen*, 418 F.3d at 1278. Paired with the clinical picture of what one would expect to see under the challenge-rechallenge paradigm, there is more than "a mere showing of a proximate temporal relationship." *Id.*

Respondent also points to *de Bazan* for requiring the disorder's etiology—or cause. Tr. at 38:5–21; *see Etiology*, Webster's Third New International Dictionary (2002) ("all of the causes of a disease or an abnormality"). The Federal Circuit in *de Bazan* stated, "the proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). In context, *de Bazan* discusses the establishment of a medically acceptable timeframe, not necessarily requiring a specific mechanism or etiology of the reliable medical theory. *Id.* Requiring the cause of a disorder to satisfy the three prongs of the causation-in-fact analysis is contradictory to what *Althen* is intended to prove—causation. *Althen*, 418 F.3d at 1278 (holding the three *Althen* prongs show "the vaccination brought about [the] injury"). The Federal Circuit conveys in *de Bazan* the proximate-temporal relationship must be medically acceptable and depends on the medical understanding of the underlying reliable theory because the theory affects the timeline of the onset of symptoms. 539 F.3d at 1352. Further, it is well established "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen ex rel. Knudsen v. Sec'y of Dep't of Health & Hum. Servs.*, 35 F.3d 543, 548–49 (Fed. Cir. 1994); *see Andreu ex rel. Andreu v. Sec'y of Dep't of Health & Hum. Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (stating petitioners "need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act"). Indeed, respondent acknowledges the Federal Circuit is reluctant to require an underlying mechanism. Tr. at 30:1–6 ("[RESPONDENT]: [F]rom reviewing the Federal Circuit decisions . . . the Federal Circuit is very reluctant to impose very specific requirements of what types . . . of evidence need to be presented."). Where challenge-rechallenge is a medically acceptable theory and petitioner establishes a medically acceptable timeframe, the microscopic mechanics of the science behind the theory, though helpful at times, are not required. *See de Bazan*, 539 F.3d at 1352; *Knudsen*, 35 F.3d at 548–49.

The Special Master reviewed the caselaw surrounding the challenge-rechallenge

paradigm and determined challenge-rechallenge could be used as a reliable medical theory to satisfy prong four of *Loving*. Ruling Finding Entitlement at 47–48. The Special Master stated "the appellate authorities seem inclined to accept challenge-rechallenge as a theory," relying on *Capizzano* and *James-Cornelius*. *Id.* As discussed *supra*, Federal Circuit caselaw supports the use of the challenge-rechallenge paradigm as a reliable medical theory, so the Special Master did not err in finding challenge-rechallenge could be used to satisfy *Loving* prong four. *See Capizzano*, 440 F.3d at 1322; *James-Cornelius*, 984 F.3d at 1380; *Knudsen*, 35 F.3d at 548–49.

B. Whether the Establishment of a Challenge Event Requires the Application of *Loving* Prongs One, Two, and Three

The parties dispute whether the Special Master applied the correct legal standard in determining a challenge event. Respondent argues the Special Master "applied the wrong legal standard by erroneously determining that 'Mr. Mager's claim is not based upon the first HPV vaccination.'" 2023 Mot. for Review at 7 (quoting Ruling Finding Entitlement at 37 n.24). Respondent contends "because the claim is based on challenge-rechallenge, Ms. Mager's first vaccination was, in fact, critical to petitioner's causation theory." *Id.* Respondent, citing *Nussman*, explains the petitioner was required to establish the first HPV vaccination as a challenge event and "failure to preponderantly establish a challenge event is fatal to a claim based on a challenge-rechallenge paradigm." *Id.* at 8 (citing *Nussman v. Sec'y of Health & Hum. Servs.*, 83 Fed. Cl. 111, 120 (2008) ("There can only be a rechallenge if there was an initial challenge and associated adverse reaction.")). Implied in respondent's arguments about the Special Master applying the "wrong legal standard" is the assertion a challenge event must be established for significant aggravation. Petitioner asserts respondent's arguments "confuse[] petitioner's claim of significant aggravation with the theory of causation, which is challenge-rechallenge." Pet'r's Resp. at 14. Petitioner explains a significant aggravation claim can be solely based on the second HPV dose, but the first vaccination is critical to the theory of causation. *Id.* at 14–15.

While respondent did not argue *Loving* prongs one, two, and three are the standard to establish a challenge event in briefing, at oral argument, respondent asserted the Special Master needed to apply *Loving* prongs one, two, and three to establish a challenge event; petitioner disagreed. Tr. at 59:5–16 ("THE COURT: You argue that for that challenge event in 2007, we should apply preponderant standard to the first three *Loving* factors? [RESPONDENT]: Absolutely, yes. . . . [PETITIONER]: . . . [The Special Master did] a *Loving* analysis of significant aggravation, but I think that's beyond actually what petitioner's burden is . . . ."), 47:18–48:5 ("THE COURT: . . . [W]hat requirement is there for the 2007 challenge event? [RESPONDENT]: Factors one through three, at a minimum."). Petitioner argued the standard for establishing a challenge event is preponderance of the evidence to see if an adverse event occurred. *See* Tr. at 60:12–61:21. "A challenge is not the same thing as a significant aggravation," petitioner asserted, and therefore *Loving* prongs one, two, and three should not be the standard for establishing a challenge event. Tr. at 60:18–22. Petitioner explained "challenge-rechallenge is not a legal term" and is distinguishable from significant aggravation, which has a statutory definition. Tr. 72:16–73:8 ("[PETITIONER]: . . . If you look at any of the general definitions of challenge-rechallenge, it simply says an adverse event."). While a challenge event does look at the before and after to determine an adverse reaction, the challenge

event does not have to meet the definition of the statute, petitioner argued. *Id.* Petitioner alternatively argued, if the Court finds *Loving* prongs one, two, and three must be applied to determine a challenge event, the Special Master analyzed the first three prongs of *Loving* for the challenge event. Tr. at 59:5–16 ("[PETITIONER]: I think what should be specifically looked at is the Special Master's factual analysis.").

The Federal Circuit, in *W.C. v. Secretary of Health and Human Services*, affirmed the *Loving* framework as the correct analytical framework for off-Table significant aggravation claims. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (citing *Loving ex rel. Loving v. Sec'y of Dep't of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2009)) ("We hold that the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims."). The parties agree *Loving* is the correct framework for significant aggravation claims. Tr. at 42:5–13 ("THE COURT: . . . [W]hat is the correct legal standard for off-Table significant aggravation claims? . . . [RESPONDENT]: [The *Loving* test] is what is used to analyze a significant aggravation claim."), 44:3–5 ("THE COURT: [What is] the correct legal standard for off-Table significant aggravation claims[?] [PETITIONER]: *Loving* is the correct standard."). The *Loving* framework, as explained by the Federal Circuit, "combines the first three *Whitecotton* factors, which establish significant aggravation, with the *Althen* factors, which establish causation." *W.C.*, 704 F.3d at 1357. The Federal Circuit explained "*Whitecotton* requires the special master to compare the injured person's condition prior to vaccination with his or her current condition to determine whether a significant aggravation occurred." *Id.* at 1356 (citing *Whitecotton ex rel. Whitecotton v. Sec'y of Health & Hum. Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996)). The comparison of the two conditions is "practically inherent in the term 'aggravation.'" *Whitecotton*, 81 F.3d at 1107. "*Loving* prong 3, like *Whitecotton* prong 3, *only requires a comparison* of a petitioner's current, post-vaccination condition with her pre-vaccination condition." *Sharpe v. Sec'y of Health & Hum. Servs.*, 964 F.3d 1072, 1082 (Fed. Cir. 2020) (emphasis added). The *Loving* framework therefore incorporates but distinguishes significant aggravation from the theory of causation. *W.C.*, 704 F.3d at 1356–57. While significant aggravation is critical to causation, whether an injury was significantly aggravated is distinct from whether the vaccination could and did cause the injury within a reasonable timeframe. *Id.* Respondent, at oral argument, agreed there is no overlap between the significant aggravation prongs and the causation prongs. Tr. at 42:14–18 ("THE COURT: . . . [I]s there overlap between the first three factors and the last three factors of *Loving* because of the significant aggravation? [RESPONDENT]: No."). Accordingly, applying *Loving* prongs one, two, and three is not necessary to establish a challenge event. *W.C.*, 704 F.3d at 1356–57.

Pursuant to 42 U.S.C. § 300aa-13(a)(1)(A), a petitioner must demonstrate "by a preponderance of evidence the matters required in the petition." The Federal Circuit "has made clear that the applicable level of proof is not certainty, but the traditional tort standard of 'preponderant evidence,'" or "the existence of a fact is more probable than its nonexistence." *Moberly ex rel. Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1322, 1322 n.2 (Fed. Cir. 2010). The parties agree petitioner must show preponderant evidence for each prong of the *Loving* analysis. Tr. at 54:17–24 (respondent), 57:12–23 (petitioner). *Loving* prong five—a logical sequence of cause and effect—therefore, must be shown by preponderant evidence. *Moberly*, 592 F.3d at 1322. As petitioner relies on the challenge-rechallenge paradigm for its

causation theory, petitioners must show the clinical picture of the challenge-rechallenge paradigm did occur by preponderant evidence for prong five. *Id.* The challenge event, or an adverse reaction, only requires preponderant evidence as part of *Loving* prong five. *Id.* An adverse reaction is not the same as significant aggravation. To require petitioner to satisfy the *Loving* one, two, and three prongs separately by preponderant evidence instead of *Loving* prong five by preponderant evidence improperly raises petitioner's burden of proof.[4] *See e.g., id.* Further, respondent did not point to any caselaw supporting the use of *Loving* prongs one, two, and three for a challenge event but merely indicated no case analyzed challenge-rechallenge in the context of a significant aggravation claim. *See* Tr. at 50:1–20. The statute requires petitioner to prove by preponderant evidence causation, including the establishment of a challenge event after the administration of a vaccine. § 300aa-13(a)(1)(A); *W.C.*, 704 F.3d at 1357; *Sharpe*, 964 F.3d at 1082; *Moberly*, 592 F.3d at 1322. The Court addresses *infra* the question of whether the record supports a challenge event.

C. Challenge Events in the Federal Circuit and Court of Federal Claims

Respondent argues petitioner is required to establish a challenge event to rely on the challenge-rechallenge paradigm and has not done so here. 2023 Mot. for Review at 7–9 (citing *Nussman*, 83 Fed. Cl. at 120). Respondent asserts there is no evidence supporting the presumption the 2007 pre-vaccination waking seizures were different from the post-vaccination nocturnal seizures in severity. *Id.* at 9. Respondent argues there is consequently no evidence to support the first HPV vaccination was a challenge event, i.e., Ms. Mager's seizures were worse after the first HPV dose. *Id.* Discussing the severity of the seizures, petitioner avers the record demonstrated significant aggravation following the first dose of the HPV vaccination. Pet'r's Resp. at 16.

As discussed *supra* Section V.A, the challenge-rechallenge paradigm can be used to establish causation. To prove the logical sequence of cause-and-effect using the challenge-rechallenge paradigm, "[t]here can only be rechallenge if there was an initial challenge and associated adverse reaction." *Nussman*, 83 Fed. Cl. at 120. The Court views other cases related to challenge-rechallenge as instructive.

The Federal Circuit instructed special masters to fully explain and analyze findings in relation to establishing challenge and rechallenge events in *Sanchez*. *See Sanchez ex rel. Sanchez v. Sec'y of Health & Hum. Servs.*, 809 F. App'x 843, 853–54 (Fed. Cir. 2020). In *Sanchez*, the petitioner alleged several sets of vaccinations caused a genetic condition to manifest or aggravated the underlying Leigh's syndrome. *Id.* at 847. The special master denied compensation; the Court of Federal Claims sustained the decision. *Id.* at 850. The petitioners appealed to the Federal Circuit, arguing "the special master failed to address their 'challenge-rechallenge' argument, i.e., their contention that the combination of the first

[4] This is not to say a full *Loving* analysis will never be required for a challenge event. Under these facts and because petitioner only alleges the second HPV vaccination aggravated the condition, the full *Loving* analysis for off-Table significant aggravation claims is not required for the initial HPV dose and challenge event. *See* Tr. at 157:5–11 ("[PETITIONER]: . . . Petitioner's claim is exclusively based on the second claim for compensation, based on the second vaccine, due to statute of limitations issues."). The Court does not opine on a circumstance where multiple doses are alleged to have aggravated a preexisting condition.

vaccination in February 2009, and the second vaccination, in August 2009, triggered or aggravated [the] condition." *Id.* The Federal Circuit vacated the decision and remanded the case due to a factual discrepancy. The Federal Circuit instructed the special master to revisit causation because "the challenge/rechallenge theory is not frivolous." *Id.* at 854.[5]

The Federal Circuit in *Rickett* requires petitioner's evidence to be concrete and consistent with medical records. In *Rickett*, the petitioner alleged the hepatitis B vaccination caused fibromyalgia. *Rickett v. Sec'y of Health & Hum. Servs.*, 468 F. App'x 952, 954 (Fed. Cir. 2011). The chief special master found the record did not support challenge-rechallenge; the Court of Federal Claims sustained the decision. *Id.* at 956. Petitioner appealed to the Federal Circuit, alleging "it was error to discount . . . expert testimony and reports regarding challenge-rechallenge to the extent they were based on [petitioner's] testimony." *Id.* at 958. The Federal Circuit affirmed this court because the special master did not err in "assign[ing] less weight to [the expert]'s conclusion regarding challenge-rechallenge to the extent it hinged upon [petitioner]'s testimony that was inconsistent with the medical records." *Id.* The Federal Circuit reasoned the expert, relying on the medical records, indicated evidence of "a challenge event was 'more speculative than real.'" *Id.* at 955. From *Rickett*, a petitioner's evidence must be concrete and consistent with medical records. *Id.*

The Court of Federal Claims in *Nussman* acknowledged the importance of timing in establishing a challenge event. *See Nussman*, 83 Fed. Cl. at 120. In *Nussman*, the petitioner alleged injuries from two hepatitis B vaccinations. *Id.* at 112. The special master denied the petition, finding the "petitioner did not fit within the 'challenge-rechallenge' paradigm because [the] petitioner did not experience adverse reactions to either hepatitis B vaccination." *Id.* at 116. The Court of Federal Claims agreed the petitioner's evidence on a challenge event was minimal, and the timing of the reactions did not fit within the challenge-rechallenge paradigm. *Id.* at 119–20. The court sustained the special master's denial of compensation based on the challenge-rechallenge paradigm because the petitioner had not shown, by preponderant evidence, an adverse reaction—or challenge event—to the first vaccination and therefore could not experience a rechallenge. *Id.* at 120 ("There can only be rechallenge if there was an initial challenge and associated adverse reaction."). From *Nussman*, a challenge event must be established and supported by appropriate timing. *Id.*

Challenge-rechallenge failed in *Bast* because the asserted symptoms did not meet medical standards for challenge and rechallenge events. In *Bast*, this court sustained the special master's rejection of the petitioner's rechallenge argument. *[M.S.B.] ex rel. Bast v. Sec'y of Health & Hum. Servs.*, 117 Fed. Cl. 104, 126 (Wolski, J.), *appeal dismissed sub nom. M.S.B. ex rel. Bast v. Sec'y of Health & Hum. Servs.*, 579 F. App'x 1001 (mem.) (Fed. Cir. 2014). The special master in *Bast* found the challenge-rechallenge argument was "unavailing because petitioner offered little more than her own assertions regarding the vaccine-relatedness or the prior symptoms allegedly part of the rechallenge scenario." *Id.* (internal quotations omitted). Further, the record,

[5] On remand, the special master again denied compensation based on the timing of the symptoms and the underlying genetic mutation. *Sanchez ex rel. Sanchez v. Sec'y of Health & Hum. Servs.*, 34 F.4th 1350, 1353 (Fed. Cir. 2022). The Court of Federal Claims sustained the decision, and the petitioners appealed. The Federal Circuit held the special master's factual finding was unsupported and found the petitioners "satisfied [the] burden of showing *Althen* prongs 2 and 3." *Id.* at 1356.

and specifically the expert witness, did not discuss whether the reactions following the vaccinations met "the standards for rechallenge identified by the Institute of Medicine or, indeed, anyone." *Id.* at 127. This court noted, "While a rechallenge event may be strong evidence of causality, petitioner has failed to show that the [c]hief [s]pecial [m]aster's rejection of the rechallenge contention was arbitrary and capricious." *Id.* From *Bast*, the asserted symptoms should meet medical standards for challenge or rechallenge events. *See id.*

The *Issac* decision from this court demonstrates the importance of corroborating medical evidence and expert testimony to support the logical cause and effect of challenge-rechallenge. *See Isaac v. Sec'y of the Dep't of Health & Hum. Servs.*, 108 Fed. Cl. 743, 777 (Smith, J.), *aff'd sub nom. Isaac v. Sec'y of Health & Hum. Servs.*, 540 F. App'x 999 (Fed. Cir. 2013). In *Isaac*, this court sustained the special master's denial of compensation after finding the expert report and testimony was insufficient to support the challenge-rechallenge paradigm. *Id.* at 778–79. The special master in *Isaac* discredited the challenge-rechallenge paradigm when the "phenomenon . . . no longer [was] accepted by scientific experts as a link between" the vaccine and the injury. *Id.* at 777. In *Isaac*, without sufficient expert testimony and corroborating medical research, the special master did not find the medical theory persuasive. *Id.*

Similarly, the testimony of treating physicians supports a finding of the logical sequence of cause-and-effect. In *Capizzano*, discussed *supra*, the Federal Circuit remanded for the special master to consider the opinions of the treating physicians because "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 (quoting *Althen*, 418 F.3d at 1280).

Reading the statute and applying the principles of caselaw, to establish a challenge event by preponderant evidence, a special master must look at the whole record in the totality of the case to determine if more likely than not a challenge event—an adverse reaction—existed. While there is not one fact dispositive of an adverse reaction—nor a requirement to prove a certain number of factors—certain facts may assist a special master when determining whether the challenge event was more likely than not: (1) the timing of the onset of symptoms with a timeframe medically acceptable; (2) the timing of the rechallenge event; (3) the severity of symptoms following each of the vaccinations; (4) known adverse reactions; (5) similarities in symptoms and timing after each of the vaccinations; and (6) the similarities of etiologies and nature of conditions. *See Capizzano*, 440 F.3d at 1326; *Sanchez*, 809 F. App'x at 854; *Rickett*, 468 F. App'x at 958; *Nussman*, 83 Fed. Cl. at 120; *Bast*, 117 Fed. Cl. at 126–27; *Isaac*, 108 Fed. Cl. at 777–79. As prescribed by the Vaccine Act, facts must be supported by at least medical records or medical opinion, including treating physicians and expert testimony. *See Capizzano*, 440 F.3d at 1326; *Sanchez*, 809 F. App'x at 854; *Rickett*, 468 F. App'x at 958; *Nussman*, 83 Fed. Cl. at 120; *Bast*, 117 Fed. Cl. at 126–27; *Isaac*, 108 Fed. Cl. at 777–79. At oral argument, petitioner agreed with the list of non-exclusive factors, as long as it does not elevate the burden of proof. *See* Tr. at 142:4–144:8. Respondent also agreed with the non-exclusive factors but acknowledged challenge-rechallenge is "fundamentally a temporal relationship." Tr. at 144:16–17. With the listed factors derived from caselaw as a guide, the Court next reviews the Special Master's decision to determine if the Special Master's determination of a challenge event is arbitrary and capricious.

VI. Whether the Special Master Erred in Determining Petitioner Satisfied *Loving* Prongs Five and Six

After determining the Special Master did not err in allowing petitioner to use the challenge-rechallenge paradigm, *see supra* Section V, the Court reviews the Special Master's determination of causation. While the Special Master determined the proximate temporal relationship first, the Court reviews the Special Master's analysis of the challenge event, *Loving* prong five, *infra* Section VI.A, and then looks at the Special Master's analysis of *Loving* prong six, the proximate temporal relationship, *infra* Section VI.B.

A. Whether the Special Master Erred in Determining Petitioner Established a Challenge Event for *Loving* Prong Five

The parties agree a challenge is an adverse reaction to a foreign antigen—in this case a vaccine—and must be established by petitioner to rely on the challenge-rechallenge paradigm. Tr. at 68:1–9 ("THE COURT: [I]n order to establish a challenge event, does there have to be an adverse reaction to a vaccination? [PETITIONER]: An adverse reaction to whatever it is, in this instance, a vaccination, yes. . . . [RESPONDENT]: Certainly. [Respondent] agrees that's necessary."); *see* 2023 Mot. for Review at 7–9 (citing *Nussman v. Sec'y of Health & Hum. Servs.*, 83 Fed. Cl. 111, 120 (2008)). The parties, however, disagree on whether the Special Master adequately analyzed the alleged challenge event.

The 2007 seizures are central to the dispute between the parties. Respondent asserts there is no evidence supporting a presumption the 2007 waking seizures were different from nocturnal seizures in severity. 2023 Mot. for Review at 9. Respondent argues there consequently is no evidence to support the first HPV vaccination was a challenge event, i.e., Ms. Mager's seizures were worse after the first HPV dose. *Id.* At oral argument, respondent argued the Special Master failed to create an adequate record regarding the waking seizure of 14 November 2007 and all of respondent's arguments, which in turn violates VRCFC 3(b)(2).[6] Tr. at 155:10–14, 156:4–16 ("[RESPONDENT]: . . . [T]he argument was made in my post-hearing brief to the Court that [Dr.] Shafrir's casting this November 14th waking seizure as being a significant aggravation was not supported by the evidence in the record. And [the Special Master] didn't analyze it, he didn't address it, there's no discussion of . . . how he weighed that evidence."). Respondent further argued the Special Master deemphasized the 2007 waking seizure because it "wasn't part of [the] claim." Tr. at 156:17–21 ("[RESPONDENT]: . . . I would submit that because [the Special Master] made a determination that [the 2007 waking seizure] was less significant due to the statute of limitations, that [the 2007 waking seizure] wasn't part of [the] claim, [the Special Master] didn't feel that he had to analyze whether or not there was a significant aggravation. . . .").

Respondent argues the 14 November 2007 seizure was important because it was not factually a challenge event. Respondent asserts, given the Special Master's finding of a preexisting seizure disorder, there is no significant difference before and after the 14 November

[6] VRCFC 3(b)(2) details the role of the special master in "creating a record sufficient to allow review of the special master's decision."

2007 vaccination and therefore no challenge event. *See* Tr. at 111:14–112:8 ("THE COURT: So your argument . . . is that there's nothing significantly different about November 14th, 2007. [RESPONDENT]: Other than the fact that she was awake, the description of the seizure from Dr. Shafrir was that this seizure was not severe, and that none of her seizures were severe. . . . There's no way to discern that [the muscle soreness, drooling, enuresis, and tongue-biting were] not a generalized tonic-clonic seizure that she was having nocturnally. There's no basis to infer one way or the other. . . . [T]hat is the factual problem in this case. The only difference that we know is that on the 14th of November, she was awake."). Respondent refers to petitioner's expert testifying the 14 November 2007 "seizure was not severe, and that none of her seizures were severe." *Id.* The lack of change in severity therefore fails to establish a challenge event, according to respondent. *See id.*

Petitioner claims respondent "mischaracterizes the Special Master's assertion as irrelevant," but "the Special Master is merely stating that [p]etitioner is not claiming an independent injury from the first dose of HPV vaccination." Pet'r's Resp. at 14. Petitioner defends the Special Master's factual analysis by pointing to: (1) the discussion of facts; (2) Ms. Mager's health prior to and after the first vaccination; and (3) expert testimony. *Id.* at 15. Regarding the severity of the seizures, petitioner avers the record demonstrated significant aggravation following the first dose of the HPV vaccination. *Id.* at 16; *see* Tr. at 157:21–159:2 (petitioner summarizing the evidence the Special Master considered).

The Court reviews the Special Master's finding the evidence supports a challenge event using the arbitrary and capricious standard because it was a finding of fact. *See Saunders v. Sec'y of Dep't of Health & Hum. Servs.*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) (quoting *Munn v. Sec'y of Dep't of Health & Hum. Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992)). It is not the Court's role "to reweigh the factual evidence[] or to assess whether the special master correctly evaluated the evidence." *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (internal quotes omitted) (quoting *Munn*, 970 F.2d at 870 n.10). As stated *supra* Section V.C, to establish a challenge event by preponderant evidence, a special master must look at the whole record in the totality of the case to determine if more likely than not an adverse reaction existed. While no one fact is dispositive of an adverse reaction, certain facts may assist a special master when determining whether the challenge event was more likely than not.

The Special Master reviewed the timeline based on Ms. Mager's medical history in both his analysis and factual sections. *See* Ruling Finding Entitlement at 48–49; Tr. at 98:8–100:18 (petitioner explaining where the Special Master analyzed the timeline and challenge event). The Special Master laid out a chronology of events in the below table explaining Ms. Mager "experienced worse seizures within an appropriate amount of time after the vaccination to conclude that she experienced challenge-rechallenge." Ruling Finding Entitlement at 48.

Date	Event
9/14/2007	Approximate onset of tongue biting, which is evidence of a seizure. In addition, by this time, [Ms. Mager] 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.

Id. at 48–49. The chronology begins on 14 September 2007 with observations of tongue biting and bedwetting, which the Special Master determined to be "evidence of a seizure."[7] *Id.* at 48. The Special Master based his factual finding on medical records and testimonies of Ms. Mager's parents and the experts. *Id.* at 2–6 ("[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.").

Following the 2 October 2007 vaccination, the Special Master chronologized the tonic-clonic seizure on 14 November 2007. *Id.* at 48. The Special Master explained Ms. Mager "experienced a seizure and was taken to the emergency room," where she had a second seizure. *Id.* at 7–8. Based on the admission notes, "[h]er extremities shook, her eyes rolled, [and] her face turned blue briefly." Ruling Finding Entitlement at 7. The Special Master observed "[t]he histories given during this hospitalization shed some light on [Ms. Mager]'s health leading up to the tonic-clonic seizure for which she was treated in the hospital." *Id.* at 8. The Special Master acknowledged the medical records and testimony of Ms. Mager's father who indicated she was a "previously healthy [female with] new onset [of seizures]," yet medical histories also indicate Ms. Mager previously had nocturnal seizures. *Id.* The Special Master included the fact Ms. Mager was prescribed an anti-seizure medication and recommended for a follow-up with a neurologist. *Id.* at 9. Based on the medical records, the Special Master indicated Ms. Mager had a "similar tonic-clonic generalized seizure while sleeping" lasting "approximately one minute and then she was unconscious for approximately five minutes." *Id.* The medical records indicate Ms. Mager was weaned off her anti-seizure medication in March 2008 at the request of her parents. *Id.* at 9–10.

The next important event on the Special Master's timeline is the "nearly five-year period in which no seizures were reported, consistent with Dr. Shafrir's opinion on dechallenge." Ruling Finding Entitlement at 48. The Special Master explained Dr. Shafrir "emphasized that [Ms. Mager] was seizure-free for nearly five years. During this period, she likely experienced

[7] Petitioner clarified at oral argument petitioner alleged the vaccinations caused the seizure disorder or, in the alternative, significantly aggravated the seizure disorder. Tr. at 61:23–62:5 ("THE COURT: . . . Looking at the Special Master decision, page 16, footnote 12, the Special Master states the petitioner argues 'the 2012 vaccination significantly aggravated the seizure disorder,' but then he also says the 2012 vaccination caused [Ms. Mager]'s seizure disorder . . . . [PETITIONER]: We were arguing [in] the alternative."). Regardless of the theory, petitioner argued the underlying theory was the same: challenge-rechallenge. Tr. at 63:12–23 ("THE COURT: . . . [W]hat's described in the Special Master's footnote 12, is that just based on different theories . . . than where you're at now? [PETITIONER]: No. . . . [I]f the Special Master found that the seizures occurred prior to 2007, then . . . it would be a significant aggravation case. If not, then it was a new onset . . . . But we were still looking at the challenge-rechallenge."). The Special Master found the evidence "favors a finding that [Ms. Mager] was biting her tongue before vaccination" based on the statements made by Ms. Mager's parents to the neurologist, and therefore the record was analyzed as a significant aggravation claim. Ruling Finding Entitlement at 4. Petitioner now argues only a significant aggravation claim. Tr. at 67:12–25 ("THE COURT: What the Special Master says is 'the 2012 vaccination . . . caused the seizure disorder.' . . . But that's different now. . . . [PETITIONER]: Yes. Significant aggravation is what we are arguing, yes. And, again, to be clear, the 2012 [new onset argument] was simply on the placement of when [Ms. Mager's parents] thought the tongue-biting had occurred.").

stress and likely was deprived of sleep at least sometimes. However, she did not experience seizures. This seizure-free time helps Dr. Shafrir isolate the vaccinations as the triggers for [Ms. Mager]'s seizures." *Id.* at 12 (internal citation omitted). The Special Master acknowledged respondent's expert Dr. Kohrman's lack of confidence Ms. Mager "did not experience seizures during these approximately five years" but gave less weight to the assertion because the records from Dr. Budde—Ms. Mager's primary care doctor at the time—did not indicate seizures. *Id.* at 12, 12 n.10.

Review of the Special Master's decision demonstrates the Special Master relied on medical records and the testimonies of Ms. Mager's parents, Ms. Mager's treating physicians, and the experts in determining an adverse reaction followed the first HPV vaccination. Indeed, because the Special Master relied heavily on medical records and testimony, it is difficult to accuse the challenge event of being "more speculative than real." *See Rickett v. Sec'y of Health & Hum. Servs.*, 468 F. App'x 952, 958 (Fed. Cir. 2011). Unlike *Rickett*, the adverse event was well-documented and consistent with the medical records. The medical records and the testimonies of parents, physicians, and experts evidence the challenge event, whereas in *Rickett* the challenge event was mere speculation. *Id.*; *see* Tr. at 94:8–22 ("THE COURT: . . . [W]hat separates this case from *Rickett*? [PETITIONER]: Well, there is no question as to the adverse event in this case. There's no sort of amorphous presentation of a symptom. . . . [In *Rickett*,] the testimony was inconsistent with the medical records . . . .").

Further, unlike *Sanchez*, the expert's testimony is consistent with the medical records and within an appropriate challenge-rechallenge timeline, especially as it relates to the dechallenge period. *Sanchez ex rel. Sanchez v. Sec'y of Health & Hum. Servs.*, 809 F. App'x 843, 854 (Fed. Cir. 2020). At oral argument, respondent argued characterizing the five-year, seizure-free period could be misleading because nocturnal seizures were difficult to see. *See* Tr. at 153:25–155:9 ("THE COURT: . . . [W]ouldn't the absence of seizures for five years after a short period of time with three or more instances support a challenge event? . . . [RESPONDENT]: . . . [T]he problem in terms of evaluating that is you have a chronic condition. . . . [I]t's certainly not rare for somebody to go five years without experiencing a seizure. And then you have to add to that the fact that the seizures that she had previously been having were largely nocturnal. . . . She very well could have had nocturnal seizures . . . that just were not witnessed."). The Special Master, however, observed the seizure-free period, likely during some time of stress and sleep deprivation, was alluded to by the medical records. Ruling Finding Entitlement at 12. The Special Master credited the medical records as accurate and the fact there was no indication of seizures during the five-year period as evidence of the seizure-free period.

The iteration of facts before and after the first vaccination illustrates the Special Master distinguished the severity of the seizures before and after the first HPV vaccination. In *Rickett*, petitioner was reporting the same symptoms before and after the vaccination, so the timing of the symptoms did not fit into the challenge-rechallenge paradigm. *Rickett*, 468 F. App'x at 958. Respondent, at oral argument, questioned whether there was a change in the seizures because there was no record of frequency prior to the first vaccination. Tr. at 151:15–18. Petitioner emphasizes "the Special Master made a distinction in this case between the nocturnal tongue-biting . . . representing the onset of . . . the original seizure disorder prior to the 2007 vaccination, and the daytime generalized tonic-clonic seizure, which is a completely different

type of seizure." Tr. at 95:19–96:4. The Court agrees the record supports the Special Master's distinction between Ms. Mager's condition before and after the first HPV vaccination. The Special Master acknowledged the medical records and testimony indicate Ms. Mager was a "previously healthy [female with] new onset [of seizures]." Ruling Finding Entitlement at 8. After the first vaccine dose, the Special Master detailed Ms. Mager rushing to the emergency room for the first observed tonic-clonic seizure followed by a second seizure at the hospital. *Id.* at 7–8. Further, the treating physicians viewed the seizures differently, illustrated by prescribing anti-seizure medication and establishing routine care with a neurologist following the 14 November 2007 seizure. *Id.* at 9–10; *see* Tr. at 112:17–113:14 ("THE COURT: . . . [W]as the November 14th, 2007, generalized tonic-clonic seizure a significant event that was different than previous items in the record [like bedwetting, drooling, and tongue-biting]? [PETITIONER]: Yes . . . . THE COURT: . . . What in the record demonstrates that? [PETITIONER]: Because . . . [t]he treating doctors don't directly relate [the bedwetting] to [the seizures]. She has generalized soreness, but . . . we don't know what that's from. . . . [T]he parents reported back, she had woken up a couple of mornings [having] bitten her tongue, which is . . . significantly less than having a full-on generalized tonic-clonic seizure, which . . . causes you to turn blue and need to be resuscitated. If they were the same, there's . . . the serious issue as to whether she would have woken up . . . which she did in prior seizures."), 120:4–121:2 ("[PETITIONER]: . . . Dr. Sharif . . . is her pediatric neurologist after she's already been diagnosed with epilepsy. . . . That can change the entire scenario of what the seizure disorder looks like at that point . . . . [The Magers] weren't referred to a pediatric neurologist at that point [with only tongue-biting and bedwetting]. [The Magers were referred] only after a witnessed . . . generalized tonic-clonic seizure, which is different. It's a different type of seizure affecting a different part of the brain. . . . [Y]ou need to take into consideration that [Dr. Sharif's records were] post-diagnosis of the epilepsy, which she hadn't had . . . prior."). Even with the Special Master finding the seizure disorder predated the first vaccination, the Special Master's narrative of Ms. Mager's condition following the first HPV vaccination tells of a change in condition.

The challenge-rechallenge paradigm has a chicken-or-egg-type problem: should the challenge or rechallenge event be established first? Petitioner asserts "the challenge event comes first. . . . But you don't know necessarily that . . . is an adverse event to a medication . . . until the dechallenge period and a rechallenge." Tr. at 114:13–19. In other words, hindsight is used to establish the challenge event by comparing the reactions after subsequent doses of a vaccine. *See also Nussman*, 83 Fed. Cl. at 120 ("There can only be rechallenge if there was an initial challenge and associated adverse reaction."). The Special Master compared the circumstances and severity of the symptoms following the first and second HPV doses. In the Special Master's chronology, the sixth event, following the second vaccination, was "[t]he first of three seizures leading to a prescription for anti-seizure medication." Ruling Finding Entitlement at 49. Citing medical records and testimony, the Special Master found "[i]t appear[ed] that [Ms. Mager] experienced two other seizures for which she did not seek medical attention emergently" and "reported two additional seizures following her emergency room visit." *Id.* at 12–13. The similarities of symptoms in the record—mainly the occurrence of more severe seizures—following both vaccinations are indicative of the challenge-rechallenge paradigm, as the Special Master found.

The challenge analysis also looks at the timing of the adverse reactions after each of the

vaccinations. *See Nussman*, 83 Fed. Cl. at 120. The Special Master noted the period between the first HPV vaccination and seizures is 43 days; "[f]or the second HPV vaccination, the latency is 29 days." Ruling Finding Entitlement at 31–32. Respondent acknowledged, at oral argument, the Special Master analyzed the challenge related to timing but disputed the established timeframe. *See infra* Section VI.B. The timing of the adverse reactions following both vaccinations supports the establishment of a challenge event. *See Nussman*, 83 Fed. Cl. at 120.

Like in *Capizzano*, the Special Master also considered the testimony of medical professionals and expert witnesses. *See Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). Specific to treating physicians, the Special Master explained Dr. Sharif treated the first observed seizure as a different type of seizure, prescribing medication, and suggested Ms. Mager "might be a candidate for surgery." Ruling Finding Entitlement at 9. The Special Master further considered the testimony of Dr. Koehn and ultimately decided "Dr. Koehn's July 2008 statement carries less weight because Dr. Koehn expressed [his opinion the HPV vaccination was not related to the seizure] before [Ms. Mager] received her second vaccination." *Id.* at 53.

In summary, the Special Master performed a full, albeit segmented, analysis of the challenge event. The Special Master reviewed the medical records—which were consistent with the opinions of the treating physicians—and the testimony of expert witnesses. From his analysis of the record, the Special Master determined the 2007 HPV vaccination constituted an adverse event and consequently a challenge event when viewed in tandem with the symptoms following the 2012 HPV vaccination; the record supports the establishment of a challenge event by preponderant evidence. *See Capizzano*, 440 F.3d at 1326; *Sanchez*, 809 F. App'x at 854; *Rickett*, 468 F. App'x at 958; *Nussman*, 83 Fed. Cl. at 120; *[M.S.B.] ex rel. Bast v. Sec'y of Health & Hum. Servs.*, 117 Fed. Cl. 104, 126–27, *appeal dismissed sub nom. M.S.B. ex rel. Bast v. Sec'y of Health & Hum. Servs.*, 579 F. App'x 1001 (mem.) (Fed. Cir. 2014); *Isaac v. Sec'y of the Dep't of Health & Hum. Servs.*, 108 Fed. Cl. 743, 777–79, *aff'd sub nom. Isaac v. Sec'y of Health & Hum. Servs.*, 540 F. App'x 999 (Fed. Cir. 2013). The Special Master did not err in finding a challenge event, nor did the Special Master violate VRCFC 3(b)(2).

B. Whether the Special Master Erred in Determining Petitioner Satisfied a Proximate Temporal Relationship for *Loving* Prong Six

The parties dispute the proximate temporal relationship established by the Slade article and supported by the Vaccine Injury Table. Respondent argues the determination "the timing here supports a finding that Ms. Mager experienced a challenge event following her October 2, 2007 vaccination is also deeply flawed." 2023 Mot. for Review at 12. Respondent asserts the Slade article, which the Special Master relied upon for a "window of plausibility," is not "related to the alleged injury in this case." *Id.* Additionally, respondent points out petitioner's expert "had no opinion as to what made [four] to 42 days 'biologically plausible.'" *Id.* Respondent also criticizes the Special Master's citation of the Vaccine Injury Table as support for the timing. *Id.* at 12–13. Respondent acknowledges the Vaccine Injury Table may be helpful but argues "the Special Master did not explain how the Table timeline for onset of GBS following influenza vaccination is relevant to the development of waking seizures following an HPV vaccination." *Id.* at 13. Respondent contends the Special Master did not "provide[] a rational basis for

selecting a timeframe generally ascribed to the development of a peripheral demyelinating condition—GBS—as opposed to some other timeframe contained in the Vaccine Injury Table." *Id.* at 14. Respondent specifically disputes the timing of the second HPV dose supporting a rechallenge event. 2023 Mot. for Review at 14. Respondent argues the review articles relied upon by petitioner's expert are contrary to the facts, and the Special Master erred in giving them credence. *Id.* at 15. Respondent asserts the "Special Master further erred in rejecting the testimony of respondent's expert immunologist, Dr. Fujinami, as to timing." *Id.* at 15 n.4.

In defending the Slade article, petitioner explains "GBS is, in fact, an autoimmune disease" and a GBS comparison is therefore applicable as evidence of the timing being "biologically plausible." Pet'r's Resp. at 17. Petitioner asserts while the Vaccine Injury Table is "not dispositive," it "can be properly relied upon" as the Special Master did after citing cases using the Vaccine Injury Table as support for timing. *Id.* at 18. Petitioner contends the Special Master's choice of the GBS-flu vaccine temporal window was not arbitrary and capricious because "it was based on expert testimony and scientific studies" and provided "additional[] though unnecessary support." *Id.* at 18–19. Petitioner argues the Special Master was allowed to extend the support timeline by one day because the Federal Circuit "has admonished special masters not to set 'hard and fast deadlines.'" *Id.* at 19 (quoting *Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1383–84 (Fed. Cir. 2015)). Petitioner rebuts respondent's implications the Special Master "failed to consider Dr. Fujinami's testimony" and states the Special Master correctly observed neither of the respondent's experts "addressed timing in their original or supplemental reports" or rebutted the timing proposed by petitioner. *Id.*

At oral argument, the parties disagreed on the persuasiveness of Slade. Respondent argued Slade is unpersuasive because "Slade actually didn't even report a single instance of a seizure following the HPV vaccination." Tr. at 160:9–25. Respondent, however, stated, "there is reference to seizures, but there's no timeframe of when they were reported, and it's not clear whether or not the onset of seizures was even reported to the authors, but there's nothing in there that would support 42 days." Tr. at 160:20–25. Respondent argued against Slade as persuasive evidence because the study "only reference[s four to 42 days] with respect to reports in the system of transverse myelitis and [GBS]," and therefore the authors "did not in any way, shape, or form apply that medically plausible timeframe to all of the incidents that they were reporting on." Tr. at 161:25–162:2, 162:13–15. The broad timeframe in Slade, according to respondent, does not account for Ms. Mager's specific adverse reaction. *See* Tr. at 167:16–168:1. Respondent argued a generalized window of adverse reactions is not supported by law. Tr. at 167:6–15 ("[RESPONDENT]: . . . [A] general causal window of anything that's 42 days . . . I don't believe would satisfy *Althen* prong three, especially given the fact that there's not a single report here or anywhere in the record of a seizure following a vaccination . . . ."). Petitioner asserted the Slade article is persuasive because it talks about "an autoimmune reaction to an immunization, and that's what we're referring to here. . . . It's the type of reaction and how long that reaction takes." Tr. at 165:2–6. Petitioner further said it would be impossible to have studies with an exact timeline to show causality because the Food and Drug Administration would pull the vaccine prior to such a severe result. Tr. at 165:11–25.

Additionally, at oral argument, the parties contested whether the Vaccine Injury Table can be used. Petitioner clarified the Special Master did not rely entirely on the Table to establish

a medically acceptable timeline; the Special Master rather used the Table as supporting evidence of the timeframe established in Slade. Petitioner explained, "The development of the timing required for an onset of an autoimmune reaction is similar . . . in both instances [because they are both autoimmune]." Tr. at 166:7–11. Dr. Shafrir, in citing the Vaccine Injury Table, pointed to "another example where that type of timing for autoimmune reaction has been accepted as medically appropriate." Tr. at 166:12–16. Respondent argued "it's fairly well understood . . . in the law that the petitioner cannot rely on similar conditions or timeframes within the Table to make out a causation in fact claim. . . . [I]f they can't rely on similar conditions and timeframes, then certainly it's not appropriate for the Special Master to rely on dissimilar injuries and dissimilar timeframes." Tr. at 141:8–14. Respondent also emphasized the Stanley study, which spoke to the development of antibodies following the HPV vaccination, rebuts the four to 42 days timeframe. Tr. at 166:20–167:3.

Loving prong six, or the proximate temporal relationship prong, "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). "Strong temporal evidence is even more important in cases involving contemporaneous events other than the vaccination, because the presence of multiple potential causative agents makes it difficult to attribute 'but-for' causation to the vaccination." *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1358 (Fed. Cir. 2006). As the Federal Circuit has cautioned, and as discussed *supra* Section V.A, an underlying biological mechanism is not required by the Vaccine Act.

The Special Master first relied on the Slade article to establish a medically acceptable timeline. Ruling Finding Entitlement at 37 (citing Slade, *supra*, at 754). The Special Master found "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 [four] to 42 days as biologically plausible." *Id.* The Special Master stated Dr. Shafrir "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 32. The Special Master also noted respondent's two experts did not "question[] the timing in their responsive reports," and respondent did not challenge the timing in pre-hearing briefing. *Id.* at 32–33. The Special Master explained "the Slade study, by itself, justifies crediting Dr. Shafrir's opinion regarding timing." *Id.* at 37.

The objective of the Slade article was "[t]o summarize reports to the Vaccine Adverse Event Reporting System (VAERS) following receipt of [the quadrivalent HPV vaccine (qHPV)]." Slade, *supra*, at 750. Slade and his contributing authors "review[ed] and describe[d] adverse events following immunization (AEFIs) reported to VAERS, a national, voluntary, passive surveillance system. . . . Additional analyses were performed for some AEFIs in prelicensure trials, those of unusual severity, or those that received public attention." *Id.* Respondent asserts the study is unpersuasive because it is not specifically narrowed to Ms. Mager's specific symptom of seizures. The fact the Slade article encompasses many adverse events does not make it unpersuasive. The parties agree challenge-rechallenge is an adverse reaction. The Slade article details the spectrum of adverse reactions. *Id.* The Slade article therefore encompasses the many adverse outcomes associated with a challenge-rechallenge

paradigm. To require "medical literature or epidemiological evidence to establish causation" is contrary to the Vaccine Act—nonetheless to require symptom-specific medical literature. *Andreu ex rel. Andreu v. Sec'y of Dep't of Health & Hum. Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009).

The timeframe relied upon in Slade is not randomly selected either. The study reviewed reactions from the HPV vaccination "[b]ased on a 6-week window of biological plausibility after immunization." Slade, *supra*, at 751. Slade noted "[g]iven the association of GBS with the 1976 swine influenza vaccine and more recently with quadrivalent meningococcal conjugate vaccine, there has been concern regarding the possibility of an association between GBS and other vaccines, including qHPV." *Id.* (footnote omitted). At oral argument, respondent attempted to discredit Slade because of the now discredited Pollard Selby study. *See* Tr. at 21:15–22:21. Petitioner argued the fact the Pollard Selby study relating to challenge-rechallenge was discredited for GBS and tetanus does not discredit the Slade article because "challenge-rechallenge is [a] completely . . . independent thing that can be applied to any medication or anything." Tr. at 138:21–23. Respondent further did not proffer evidence rebutting the Slade article. Ruling Finding Entitlement at 32–33. Given the evidence in front of the Special Master, it was reasonable to credit the Slade article. *See Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (quoting *Munn*, 970 F.2d at 870 n.10) (stating the court should not "reweigh the factual evidence[] or . . . assess whether the special master correctly evaluated the evidence").

In addressing Dr. Fujinami's opinions regarding timing, the Special Master stated his "opinions regarding timing are not credited" because Dr. Fujinami "did not indicate that timing was a problem in his reports," and the "lack of disclosure is inconsistent with how the Vaccine Program usually operates." Ruling Finding Entitlement at 38–39. The Special Master gave less weight to Dr. Fujinami's opinions because he "did not present literature supporting his position." *Id.* at 39. The Special Master acknowledged literature is not required in Vaccine cases but also noted "a scientific theory that lacks any empirical support will have limited persuasive force." *Id.* at 39 (quoting *Caves v. Sec'y of Dep't of Health & Hum. Servs.*, 100 Fed. Cl. 119, 134 (2011), *aff'd sub nom. Caves v. Sec'y of Health & Hum. Servs.*, 463 F. App'x 932 (Fed. Cir. 2012)) (citing *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1280–81 (Fed. Cir. 2005)).

The Court's role is "not [to] reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses—these are all matters within the purview of the fact finder." *Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011). The credibility of witnesses lays squarely within the purview of the Special Master, and the Court cannot "reweigh" the credibility but can only look to see if the Special Master's decision was arbitrary and capricious. *Id.* The Special Master explained Dr. Fujinami's testimony was not credited because of procedural issues and lack of support from other sources; the Special Master's weighing of Dr. Fujinami's testimony was not arbitrary and capricious. *See id.*

Respondent also argues the Special Master could not rely on the Vaccine Injury Table. The Special Master, however, did not rely on the Vaccine Injury Table to establish a timeframe

but stated "the Slade study, by itself, justifies crediting Dr. Shafrir's opinion regarding timing" and "additional support comes from the Vaccine Injury Table." Ruling Finding Entitlement at 37. The Special Master expressly stated the Vaccine Injury Table is "additional support," and the Court does not find the reference to the Vaccine Injury Table to be arbitrary and capricious.

The Special Master found, after crediting a four to 42 day timeframe, the timeframe "may be reasonably expanded to 43 days." *Id.* at 38 (citing *Paluck*, 786 F.3d at 1383–84). Given the Special Master found the Slade article persuasive and the onset of seizures was within the medically acceptable timeframe, the Special Master was not arbitrary and capricious to conclude petitioner satisfied *Loving* prong six; the Court finds no error. *See Porter*, 663 F.3d at 1249.

VII. Whether Petitioner Showed Ms. Mager's Death Was a Sequela of the Significantly Aggravated Seizure Disorder to Satisfy a *Prima Facie* Case of Causation

The parties dispute whether the burden properly shifted to respondent. Hidden in respondent's argument is the notion of requiring petitioner to prove not only the vaccination significantly aggravated the seizure disorder but also the significantly aggravated seizure disorder caused Ms. Mager's death. The Court notes respondent's Motion for Review dedicated a mere three paragraphs to the unrelated factor issue, much of which was block quotes from other sources. At oral argument, respondent expounded on the argument. *See* Tr. at 168:20–170:1. In addressing the argument, the Court first determines if petitioner properly established the HPV vaccine was a "substantial factor" in Ms. Mager's death, causing the burden to shift to respondent.

Respondent argues "the Special Master erroneously shifted the burden to respondent to disprove . . . Ms. Mager's September 11, 2012 HPV vaccination caused her death." 2023 Mot. for Review at 19. Respondent, referencing petitioner's expert, asserts Ms. Mager's death was a result of SUDEP and not correlated to the vaccination. *Id.* at 20. Respondent argues because petitioner's expert "disavowed any relationship between Ms. Mager's vaccinations and her SUDEP, and given the Special Master's finding that the HPV vaccine did not cause Ms. Mager's epilepsy, the Special Master erred in shifting the burden to respondent to establish that Ms. Mager's death was the natural result of her epilepsy and finding respondent failed to meet that burden." *Id.*

Petitioner, citing *Walther*, explains "the burden shifts to [respondent] under the 'factor unrelated' inquiry to show that the pre-existing condition caused the significantly worsened condition." Pet'r's Resp. at 23 (citing *Walther v. Sec'y of Health & Hum. Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007)). Petitioner maintains he met the burden of proof, and therefore the burden "shifts to [r]espondent to prove an alternative cause, e.g. the natural course of the disease, for either [Ms. Mager's] epilepsy post the second vaccination or her subsequent death." *Id.* Petitioner asserts the Special Master "discussed the evidence related to [Ms. Mager's] death specifically[,] found the [r]espondent failed to meet [its] burden," and therefore did not err. *Id.* at 24 (citing Ruling Finding Entitlement at 55).

At oral argument, respondent explained: petitioner had not met the burden of proving the vaccination caused Ms. Mager's death, and therefore the burden should not have shifted.

Respondent's contention at oral argument centered around Dr. Shafrir's testimony, which asserted there was no correlation between the HPV vaccine and SUDEP. Respondent consequently argued petitioner did not connect Ms. Mager's death with the vaccination and did not meet his burden of causation. Tr. at 168:20–169:6 ("[RESPONDENT]: [A]s you say that back to me, that's not . . . the point that I'm making. . . . [T]he point is that the death does not appear to be a consequence of the vaccination. . . . [A] death is an injury. The petitioner bears the burden of proving that the vaccine brought about the injury. . . . [I]n this case the only causal theory was challenge/rechallenge. And if you accept that theory and you accept 42 days, well, the death did not occur within 42 days. So how does the vaccine cause the death?"). Petitioner explained SUDEP is associated with epilepsy, and the vaccination significantly aggravated the epilepsy, so the death is connected to the vaccine, albeit once removed in the chain. Petitioner also asserted, from *Sharpe*, death is not a defense. *See* Tr. at 172:2–15 ("[PETITIONER]: . . . [T]he defense of a natural course of a disease[] is not a defense under the Federal Circuit's ruling in *Sharpe*."). Petitioner maintained the Special Master "found that the vaccine caused the significant aggravation of her epilepsy and that . . . resulted in her death." Tr. at 180:16–181:4 ("[PETITIONER]: . . . [T]he significant issue is seizure-free versus ongoing seizures . . . none of the treating doctors separated . . . her death from the seizures that she had post the second vaccination. That's the same course. THE COURT: It was all consistent. [PETITIONER]: It's all consistent, yeah. And there's no requirement, no burden on petitioner, to show that the death occurs within a short period of time following vaccination. You have to draw a direct line. There is a direct line. The Special Master found that the vaccine caused the significant aggravation of her epilepsy and that . . . resulted in her death.").

To successfully establish a vaccine injury claim, a petitioner must show the vaccination was the cause of the injury or death. *H.L. ex rel. A.I. v. Sec'y of Health & Hum. Servs.*, 715 F. App'x 990, 994 (Fed. Cir. 2017) (citing *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1341 (Fed. Cir. 2010)); 42 U.S.C. § 300aa-11(c). For the Vaccine Program to compensate a petitioner, the Vaccine Act requires the petitioner, by preponderant evidence, to "demonstrate[] that the person who suffered such injury or who died . . . sustained, or had significantly aggravated, any illness, disability, injury, or condition not set forth in the Vaccine Injury Table which was caused by a vaccine." § 300aa-11(c)(1)(C)(ii)(I). In short, to recover for significant aggravation, petitioner must prove the vaccine caused the significant aggravation of the underlying disease and death. *See Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351 (Fed. Cir. 2019).

Federal Circuit caselaw has long established "[r]ecovery for a death following a . . . vaccination based on a Table claim is conditioned upon the death being a *sequela of an illness or condition* listed in [the Vaccine Injury Table] 'which arose within the time period prescribed' in the Table for that illness or condition." *Hellebrand v. Sec'y of Dep't of Health & Hum. Servs.*, 999 F.2d 1565, 1570 (Fed. Cir. 1993) (emphasis added). In *Hellebrand*, petitioner alleged a Table vaccine-related injury which ultimately resulted in sudden infant death syndrome ("SIDS"). *Id.* at 1566. The special master found the petitioner was not entitled to recovery, while this court determined the petitioner was entitled to recovery. *Id.* at 1567–69. On appeal, the Federal Circuit held the petitioner could not recover for the death of the child because the petitioner was required to show the injury occurred within the timeframe in the Table and the subsequent "death was a sequela of" the injury. *Id.* at 1570.

The Vaccine Act allows for compensation for both Table and off-Table injuries and subsequent deaths which are caused or significantly aggravated by a vaccination. *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005) ("The Act provides for the establishment of causation in one of two ways: through a statutorily-prescribed presumption of causation upon a showing that the injury falls under the Vaccine Injury Table . . . or where the complained-of-injury is not listed in the Vaccine Injury Table . . . , by proving causation in fact . . . ."). It is therefore a natural extension of *Hellebrand* to require "death [to be] a sequela of" the off-Table injury for petitioner to be entitled to compensation of a death. *Id.*; 999 F.2d at 1570. Where the aggravated condition ultimately leads to death, petitioner must provide a link between the aggravated state and the death. *Hellebrand*, 999 F.2d at 1569–70; *see* 42 U.S.C. § 300aa-11(c)(1)(A), (c)(1)(C)(i), (c)(1)(C)(ii)(I); *see also Shyface v. Sec'y, Health & Hum. Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999) (holding when an injury or death is found to have multiple causes, a petitioner need not prove the vaccination was the principle or predominant cause but only a "substantial factor" in causing the injury or death).

Petitioner here alleges not only significant aggravation of the underlying seizure disorder but also the aggravation of the seizure disorder ultimately caused Ms. Mager's death by SUDEP. Am. Pet. ¶ 12, ECF No. 11. Petitioner therefore needed to prove SUDEP was a sequela of Ms. Mager's off-Table aggravated seizure disorder. *See Hellebrand*, 999 F.2d at 1569–70; 42 U.S.C. § 300aa-11(c)(1)(A), (c)(1)(C)(i), (c)(1)(C)(ii)(I). As the Special Master did not directly address whether SUDEP was a sequela of Ms. Mager's aggravated seizure disorder, the Court reviews the record to determine if the record supports a finding SUDEP is the sequela of Ms. Mager's aggravated seizure disorder.

To understand the application of death as a sequela of a condition, it is helpful to understand SUDEP in comparison to a directly caused vaccine injury allegation, like SIDS, where the petitioner must show the vaccinations "cause or contribute to a . . . death." *Boatmon*, 941 F.3d at 1361 (affirming this court's denial of compensation because petitioners "failed to show by a preponderance of the evidence that vaccinations cause cytokines to provoke an abnormal brainstem serotonin response or otherwise cause or contribute to a SIDS death"). SUDEP "refers to deaths in people with epilepsy that are not from injury, drowning, or other known causes. Most, but not all, cases of SUDEP happen during or right after a seizure." CDC, *Sudden Unexpected Death in Epilepsy (SUDEP)*, (last visited June 1, 2023) https://www.cdc.gov/epilepsy/communications/features/sudep.htm (citing Orrin Devinsky, *Sudden, Unexpected Death in Epilepsy*, 365 NEW ENG. J. MED. 1801–11 (2011)). SIDS, in contrast, "is defined as 'the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation'" and requires a three-factor model to be satisfied. *Boatmon*, 941 F.3d at 1355. For SIDS to be compensated, a petitioner must "show by a preponderance of the evidence . . . vaccinations can be exogenous stressors," the third factor required by the SIDS model. *Id.* at 1362. Whereas SUDEP is a death associated with epilepsy, death from SIDS is not associated with a particular underlying condition but requires all three factors be met. In other words, SUDEP is a medically accepted consequence of epilepsy and is properly once removed from a separate factor causing the epilepsy or increasing the severity of the underlying epilepsy. Death from SUDEP can be a sequela of seizures, caused or aggravated by a vaccination. To allege a vaccination caused SIDS, death from SIDS must be directly linked

to the vaccination. The government contends petitioner should be required to directly connect Ms. Mager's HPV vaccination to her death; the Court accordingly reviews precedential SIDS caselaw to confirm the differences between a death alleged to have been directly caused by a vaccination, such as SIDS, and a death alleged to have been a sequela of a vaccination, such as SUDEP.

In *Boatmon*, the parents of a deceased child alleged several vaccinations caused the death of their child. *Id.* at 1353–54. The special master relied on expert testimony positing SIDS is "multifactorial," occurring "when: (1) an infant in a critical development period; (2) possessing an underlying vulnerability; (3) encounters an exogenous stressor." *Id.* at 1355. The petitioners' expert theorized "receiving a vaccine can be an exogenous stressor for SIDS because it[] prompts the upregulation of cytokines." *Id.* at 1356. The respondent "disagreed that upper respiratory infections—and by [the expert]'s extension, vaccinations—act as neurochemical exogenous stressors." *Id.* The special master nevertheless found causation based on risk factors. *Id.* at 1356–57 (internal citation omitted) ("On Althen prong one, the [s]pecial [m]aster adopted [the expert]'s extension of the Triple Risk Model, concluding that 'vaccines can . . . play a critical role . . . by stimulating the production of inflammatory cytokines.' We note for clarity that the [s]pecial [m]aster also stated that 'I have not concluded that vaccines present a substantial risk of SIDS. In fact, the evidence is to the contrary.'"). The Court of Federal Claims reversed because the expert testimony was not supported by a sound and reliable medical theory, and the petitioners appealed. *Id.* at 1357–58. The Federal Circuit affirmed the decision from this court because the petitioners failed to show the vaccinations contributed to the risk of SIDS and the ultimate death from SIDS through a reliable, reputable medical theory. *See id.* at 1359–63. Specifically, in *Boatmon*, the petitioners' theory did not properly link the vaccinations to the exogenous stressor factor of the Triple Risk Model for SIDS through a reliable or plausible medical theory.[8] *Id.*

Respondent suggests a person with an underlying seizure disorder would never be able to recover under the Vaccine Act for SUDEP because of the inherent risk of SUDEP. *See* Tr. at 172:25–173:11 ("[RESPONDENT]: . . . [T]he death is related to the epilepsy. And since we know that her epilepsy predates both of her vaccines, it's not the cause of her epilepsy. If the vaccine caused her epilepsy and she would have died from epilepsy, you would see that causal

[8] SIDS research supports a Triple Risk Model for factors contributing to SIDS. *Boatmon*, 941 F.3d at 1355–56. While the Federal Circuit credited the Triple Risk Model, the Federal Circuit did not agree with the petitioners' extension of the theory "to include vaccination-induced cytokine activity in the list of exogenous stressors as [the expert] propose[d]." *Id.* at 1360. The Federal Circuit explained, "Petitioners have not shown that their theory that vaccinations can be an exogenous stressor under the Triple Risk Model of SIDS is a sound and reliable medical theory." *Id.* Indeed, the Federal Circuit, after reviewing the studies proffered to support the extension of the Triple Risk Model, held the "studies do not provide support . . . because they do not show that that cytokine activity is capable of impacting the brain's 5–HT system." *Id.* at 1362. The Federal Circuit stated "[w]e have consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Id.* at 1360 (citing *Moberly ex rel. Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)). Both the special master and the expert found the theory only "plausible," so the Federal Circuit held "[t]he [s]pecial [m]aster erred in allowing a theory that was at best 'plausible' to satisfy the [p]etitioners' burden of proof." *Id.* In summary, the Federal Circuit rejected the extension of the Triple Risk Model to link the vaccinations to the death from SIDS. *Id.* at 1361 ("The [s]pecial [m]aster erred in adopting an unsound and unreliable theory that constitutes a significant extension of the Triple Risk Model in the absence of any indicia of reliability.").

chain. But the epilepsy . . . predates the HPV vaccine. The vaccine didn't cause her epilepsy. And according to Dr. Shafrir, SUDEP can happen essentially anytime, anywhere, five years later, 10 years later, 20 years later, whether you have high risks, whether you take your medication, whether your seizures are controlled or uncontrolled."). The Federal Circuit in *Sharpe* addressed a similar issue where the respondent argued the underlying genetic condition barred recovery.[9] *Sharpe*, 964 F.3d at 1087. The Federal Circuit rejected the argument, reasoning: "To uphold the [s]pecial [m]aster's finding would effectively allow the government to prevail under the 'factor unrelated' inquiry with mere proof of a gene mutation. As a result, children with gene mutations will be shut out from the Vaccine Injury Program. Congress did not intend such a result." *Id.* Likewise, the unfortunate circumstance of having a preexisting seizure disorder and developing a seizure disorder should not bar a whole population of persons. *See id.* Rather, in the case where the death is unexplained but has certain risk factors, petitioner must show how the aggravated condition increases the risk of death. *See Boatmon*, 941 F.3d at 1359–63.

Unlike *Boatmon*, petitioner put forth a reliable medical theory, *see supra* Section V, so the Court looks to whether the record supports an increased risk of SUDEP following vaccination. In the present case, like *Boatmon*, respondent claims petitioner did not connect the vaccination to the ultimate death of Ms. Mager. Tr. at 175:9–10 ("[RESPONDENT]: . . . [T]he death did not occur within 42 days."). Respondent's contention petitioner did not meet his burden of proof is based on Dr. Shafrir's statements made during the compensation hearing. Dr. Shafrir stated:

> Her death may have not happened if she was able to get better treatment. Unfortunately, she kept having insurance say if she could go to the doctor and everything. So she had SUDEP. SUDEP could have occurred, could not have occurred, could have occurred after a few months with epilepsy, could have occurred after 20 years of epilepsy. *So the SUDEP is not correlated to the vaccination or to anything else.* SUDEP is a terrible accident or complication of having epilepsy.

8 Mar. 2022 Compensation Hr'g Tr. at 355:3–12, ECF No. 216. The case is different than *Boatmon*—in *Boatmon*, the petitioners' theory necessitated the vaccination contributed to SIDS as the third factor exogenous stressor; Ms. Mager's case only requires petitioner to show the vaccination aggravated the seizure disorder and the aggravated seizure disorder contributed to the risk of a seizure death—SUDEP. *See Boatmon*, 941 F.3d at 1359–63.

Statements throughout the record, from both parties, support Ms. Mager having a higher risk of SUDEP, unlike *Boatmon*. Both experts agree there are several risk factors associated with SUDEP, including "convulsions at night within the previous year . . . liv[ing] alone . . .

[9] Petitioner cites *Sharpe* as barring death as a defense. Petitioner, however, misreads *Sharpe*. The Federal Circuit warned in *Sharpe* "off-table claim[s] present[] the difficult but important task of determining whether a child's receipt of vaccinations significantly aggravated her seizure disorder . . . . Our case law is clear that given the complexity of a significant aggravation claim, a petitioner should not be required to disprove that a pre-existing [condition] caused her significant aggravation." 964 F.3d at 1087. The Federal Circuit held a petitioner is not required to prove the natural course of the disease during the causation-in-fact analysis. *Id.* Under *Sharpe*, it is the respondent's burden to prove the vaccination did not aggravate the underlying disorder but rather the aggravation of the disorder and ultimate death was the natural course of the disease.

using recreational drugs and alcohol . . . frequent convulsions, particularly those that occur at night," and compliance with medication. Kohrman Expert Report at 15 (quoting study), ECF No. 183-1; *see* Shafrir Reply Report at 1–2 ("Ms. Mager tragically died of SUDEP . . . . SUDEP is in the phenomenon in patients with epilepsy. It can occur in patients whose epilepsy is not that severe, although the risk is increasing in more severe forms of epilepsy, in intractable epilepsy that is not responding to treatment and in patients who are not compliant with [their] medications. Ms. Mager suffered SUDEP as a result of the acquired autoimmune epilepsy, which was the result of her repeated HPV vaccination . . . ."). Dr. Kohrman, during the compensation hearing, acknowledged Ms. Mager was at "greater risk for seizure being up until 4:00 a.m. and then going to sleep. . . . [S]he was having seizures in her sleep that she didn't recognize. . . . [S]he had an uncontrolled epilepsy. . . . [S]he had intermittent issues with adherence to her medication, all of which put her at greater risk for sudden death." 9 Mar. 2022 Compensation Hr'g Tr. at 533:20–534:13, ECF No. 217. Dr. Shafrir acknowledged the "four major risks are nocturnal seizures, generalized seizures, poorly controlled seizures[,] and poor compliance" but "other factors [are] involved, [and] it's very, very important to know that many patients with SUDEP have no risk factors." 8 Mar. 2022 Compensation Hr'g Tr. at 331:20–332:4, 355:3–12. Dr. Shafrir wrote in his reply report, "SUDEP . . . can occur in patients whose epilepsy is not that severe, *although the risk is increasing in more severe forms of epilepsy*." Shafrir Reply Report at 1–2 (emphasis added).

The Special Master in his opinion and in the record also found Ms. Mager's risk was higher because the underlying seizure disorder was aggravated. Ruling Finding Entitlement at 48 (Ms. Mager "experienced worse seizures within an appropriate amount of time after the vaccinations"). SUDEP, by definition, is dependent on seizing; therefore increased seizure activity would naturally increase the risk of SUDEP. *See* CDC, *supra* (defining SUDEP as "deaths in people with epilepsy that are not from injury, drowning, or other known causes. *Most, but not all, cases of SUDEP happen during or right after a seizure*.") (emphasis added). The Special Master emphasized Ms. Mager's "condition was worse than her condition before the vaccination. Before the vaccination, [Ms. Mager] had not had a seizure in approximately five years and was not taking any anti-seizure medications. Afterwards, [Ms. Mager] suffered three seizures within about one month and began taking medications." Ruling Finding Entitlement at 30–31. The Special Master, looking at the medical records and relying on expert testimony, found the second dose of HPV increased Ms. Mager's risk because she began seizing again. *Id.* at 28 ("Before this vaccine, [Ms. Mager] had not suffered any seizures in nearly five years."); *see also* Shafrir Reply Report at 1–2 ("SUDEP . . . can occur in patients whose epilepsy is not that severe, although the risk is increasing in more severe forms of epilepsy . . . .").

Respondent suggested at oral argument there may have been a dechallenge period before Ms. Mager's death. Petitioner argues the dechallenge period is not relevant because the record supports ongoing seizures after the second dose. Tr. at 179:14–23 ("[PETITIONER]: Both the father and the best friend gave reports that she was having increasing seizures leading up to her death. They did that in a report to the police immediately afterwards and . . . the Special Master didn't credit those because they weren't in the medical records, but [after] only one of the subsequent seizures after the second vaccination did she go to the doctor. Most epileptics don't go to the doctor after every seizure."). The Special Master found persuasive petitioner's argument the change in the severity and the consistency of seizures also increased Ms. Mager's

risk for SUDEP. Ruling Finding Entitlement at 30 ("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.'"); *see also* Shafrir Reply Report at 1–2; Kohrman Expert Report at 15.

The Special Master contemplated other risk factors, including compliance with medication, in finding the aggravated seizure disorder increased SUDEP risk. The Special Master reasoned, "Dr. Shafrir testified that [Ms. Mager]'s 'death may have not happened if she was able to get better treatment.' A relevant factor is that [Ms. Mager] may have had poor compliance with her medication. However, according to a toxicology report, [Ms. Mager] had therapeutic levels of Keppra in her blood at the time of her death." Ruling Finding Entitlement at 54 (internal citations omitted). The Special Master found Ms. Mager was compliant with medications, based on the autopsy report, and the break-through seizures on medication indicated more severe seizures and consequently a higher risk of SUDEP. *Id.*

While the Special Master did not explicitly find death was the "sequela" of the significantly aggravated seizure disorder, the record and the Special Master's findings support the vaccination increasing the risk of SUDEP; accordingly, causation was established. *See Hellebrand*, 999 F.2d at 1570; *Shyface*, 165 F.3d at 1352 ("We adopt the Restatement rule for purposes of determining vaccine injury, that an action is the 'legal cause' of harm if that action is a 'substantial factor' in bringing about the harm, and that harm would not have occurred but for the action."). "Once a petitioner establishes her *prima facie* case by satisfying the *Althen* test, the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Hum. Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa–13(a)(1)(B)); *see also Sharpe*, 964 F.3d at 1086.

VIII. Whether the Special Master Erred in Holding Respondent Failed to Prove an Unrelated Factor Under Preponderant Evidence

As the Court finds no error in the Special Master's *Loving* analysis and the record supports death as the sequela of the significantly aggravated seizure disorder, the burden shifts to respondent. *See supra* Section VII. The Court must now determine if the Special Master erred in holding respondent did not meet the burden of proof for unrelated factor.

Respondent in its Motion for Review does not challenge the Special Master's finding respondent "has not established [Ms. Mager's death is the natural result of her epilepsy] by a preponderance of evidence." Ruling Finding Entitlement at 55; *see* 2023 Mot. for Review at 19–20. Respondent instead argues an improper shift of the burden of proof, addressed by the Court *supra* Section VII. Finding petitioner satisfied causation, the burden properly shifted to respondent to prove Ms. Mager's death was a natural course of the disease with preponderant evidence. *See Sharpe v. Sec'y of Health & Hum. Servs.*, 964 F.3d 1072, 1087 (Fed. Cir. 2020).

The Court reviews factual findings under the arbitrary and capricious standard, and it is

not the Court's role "to reweigh the factual evidence, or to assess whether the special master correctly evaluated the evidence." *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (internal quotes omitted) (quoting *Munn v. Sec'y of Dep't of Health & Hum. Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992)). To meet the burden of showing an unrelated factor, "the respondent must identify a particular factor (or factors) and present sufficient evidence to establish that it was the sole substantial factor in bringing about the injury." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Hum. Servs.*, 717 F.3d 1363, 1367 (cleaned up) (citing *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1354 (Fed. Cir. 2008); *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005)). The "Vaccine Act requires the Secretary to establish that the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged." *Deribeaux*, 717 F.3d at 1369. It is well established "a special master may find that a factor other than a vaccine caused the injury in question only if that finding is supported by a preponderance of the evidence." *Stone v. Sec'y of Health & Hum. Servs.*, 676 F.3d 1373, 1380 (Fed. Cir. 2012) (citing *Walther v. Sec'y of Health & Hum. Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007)).

In *Sanchez*, the Federal Circuit illustrated how unrelated factors relate to significant aggravation claims. *Sanchez ex rel. Sanchez v. Sec'y of Health & Hum. Servs.*, 34 F.4th 1350, 1356 (Fed. Cir. 2022). *Sanchez* involved a petitioner with Leigh's syndrome. *Id.* The respondent alleged the mutation leading to Leigh's syndrome resulted in the same progression and severity absent the vaccine. *Id.* at 1356. The Federal Circuit held the respondent "did not meet its burden to establish . . . Leigh's syndrome was the result of factors unrelated to the vaccine." *Id.* The Federal Circuit criticized the reference used by the respondent because it "provide[d] no information on how the subject's disease progressed after manifestation" or what caused the syndrome to progress the way it did. *Id.* Indeed, the Federal Circuit explained the cited reference by stating "a single example does not establish the typical progression of a disease and is not 'sufficient to disprove a medical theory that a vaccine *can* cause aggravation in *some* patients.'" *Id.* (quoting *Sharpe*, 964 F.3d at 1084).

The Special Master noted "[t]he parties did not extensively discuss the natural course of generic epilepsy." Ruling Finding Entitlement at 53. The Special Master, however, reviewed the arguments of respondent and petitioner to determine whether the outcome of Ms. Mager's epilepsy was the natural course of the disease. *Id.* at 53–55. Respondent's primary argument was Ms. Mager's significant aggravation of the underlying seizure disorder was the natural course of the disease. *Id.* at 53. This argument, the Special Master pointed out, is "premised, at least in part, on the assertion that [Ms. Mager] suffered from juvenile myoclonic epilepsy." *Id.* The Special Master credited respondent's expert, Dr. Kohrman, stating "a person with JME and who is not taking anti-seizure medication may have years without seizures and the redevelop seizures." *Id.* The Special Master, however, ultimately did not find the argument persuasive because of the Court's determination of simply a seizure disorder. *Id.*; *see Mager v. Sec'y of Health & Hum. Servs.*, 158 Fed. Cl. 136, 155–56 (2022).

Respondent's secondary argument was Ms. Mager's "death was due to the natural course of her epilepsy." Ruling Finding Entitlement at 53–54. The Special Master reviewed the evidence presented by respondent regarding SUDEP being the natural course of epilepsy. A key piece of evidence was compliance with medication. Respondent argued "people whose

epilepsies are controlled without medication can redevelop seizures unpredictably." *Id.* at 54. The Special Master, however, noted "according to a toxicology report, [Ms. Mager] had therapeutic levels of Keppra in her blood at the time of her death." *Id.* The seizures therefore should not have broken through with Ms. Mager taking medication.

The Special Master acknowledged 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 [Ms. Mager]'s epilepsy, unaggravated by the second HPV vaccination, might have progressed." *Id.* at 55. The Special Master concluded without evidence of how Ms. Mager's epilepsy might have progressed, unaggravated by the HPV vaccination, respondent's claim Ms. Mager's "death is the natural result of her epilepsy seems possible." *Id.*

In this case, like *Sanchez*, respondent was unable to "establish the typical progression of a disease" and therefore did not provide evidence "sufficient to disprove a medical theory that a vaccine *can* cause aggravation in *some* patients." *Sanchez*, 34 F.4th at 1356 (quoting *Sharpe*, 964 F.3d at 1084). To meet its burden, respondent was required to show by preponderant evidence SUDEP was the natural course of Ms. Mager's disease and therefore the "sole substantial factor" in Ms. Mager's injury; respondent did not offer evidence showing the normal course of Ms. Mager's unaggravated seizure disorder. The Special Master, weighing all the evidence, determined there was not a preponderance of evidence shown by respondent. Ruling Finding Entitlement at 53–55. The Special Master accordingly did not err because respondent did not prove an unrelated factor by preponderant evidence. *See Sanchez*, 34 F.4th at 1356 (quoting *Sharpe*, 964 F.3d at 1084); *Stone*, 676 F.3d at 1380 (citing *Walther*, 485 F.3d at 1151); *Lampe*, 219 F.3d at 1360 (quoting *Munn*, 970 F.2d at 870 n.10).

IX. Conclusion

For the foregoing reasons, the Court **DENIES** respondent's Motion for Review, ECF No. 242, and **SUSTAINS** the Special Master's Ruling Finding Entitlement, ECF No. 224. The Court **DIRECTS** the Clerk to enter judgment, pursuant to the Special Master's decision in ECF No. 240, for $365,593.02.

IT IS SO ORDERED.

s/ Ryan T. Holte
RYAN T. HOLTE
Judge