# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

**No. 17-1123V**

Filed: August 21, 2023

* * * * * * * * * * * * * * * * * * * * * * * * * * *

TREY COBB,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

* * * * * * * * * * * * * * * * * * * * * * * * * * *

*Mark Sadaka*, Law Offices of Sadaka and Associates, LLC, Englewood, NJ, for Petitioner
*Debra Begley*, U.S. Department of Justice, Washington, DC, for Respondent

## RULING ON ENTITLEMENT[1]

**Oler**, Special Master:

On August 21, 2017, Jeffrey and Kimberly Cobb, filed a petition for compensation on behalf of their then minor son, Trey Cobb ("Petitioner") under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq*.[2] (the "Vaccine Act" or "Program"). The petition alleges that Trey Cobb developed narcolepsy and cataplexy (type 1 narcolepsy) that was

[1] Because this Ruling contains a reasoned explanation for the action in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

either caused by or significantly aggravated by his August 25, 2014 and August 18, 2015[3] human papillomavirus ("HPV") vaccinations. Pet. at 1; ECF No. 1.

Upon review of the evidence submitted, I find that Petitioner has preponderantly established that the HPV vaccine can cause narcolepsy and cataplexy, and that it did so in this case.

## I. Procedural History

Mr. Jeffrey Cobb and Ms. Kimberly Cobb[4] filed a petition on behalf of their son, Trey Cobb, on August 21, 2017. ECF No. 1. They filed medical records in support of their petition on August 22, 2017. Exs. 1-7. Petitioner filed additional medical records on December 12, 2017, and an affidavit from Ms. Kimberly Cobb on December 15, 2017. Exs. 8-10.

Respondent filed his Rule 4(c) Report on March 5, 2018 recommending that entitlement be denied. Resp't's Rep. at 1, ECF No. 21.

On August 15, 2018, Petitioner filed an expert report from Dr. Lawrence Steinman in support of his claim. Ex. 11. Petitioner filed Dr. Steinman's CV as Ex. 12 (hereinafter "Steinman CV") as well as supporting medical literature (Exs. 13-42).

On March 4, 2019, Respondent filed an expert report from Dr. Lawrence Brown (Ex. A) and Dr. Brown's CV (Ex. B; hereinafter "Brown CV"). On May 1, 2019, Respondent filed an expert report from Dr. Robert Fujinami (Ex. C), Dr. Fujinami's CV (Ex. D; hereinafter "Fujinami CV"), and supporting medical literature (Ex. C, Tabs 1-9). On December 30, 2019, Respondent filed additional medical literature. Ex. A, Tabs 1-20.

Petitioner filed a supplemental report from Dr. Steinman on December 30, 2019. Ex. 43. Respondent filed a supplemental response from Dr. Fujinami on April 28, 2020 (Ex. E) and two additional pieces of medical literature (Ex. E, Tabs 1-2).

I conducted an entitlement hearing via Zoom on September 21, 2021. *See* Minute Entry dated 9/21/2021. Petitioner presented his own testimony and Dr. Steinman provided expert testimony. Tr. at 3. Respondent presented testimony from Drs. Brown and Fujinami. *Id.*

---

[3] The record from Petitioner's well exam where he received his third HPV vaccine is unclear as to the date of the appointment. The "charted date/time" is listed as 08/18/2015 14:17. Ex. 6 at 30. However when Petitioner's vital signs were measured at this appointment, the record documents they were taken on 08/17/2015 at 14:13. *Id.* Further, Dr. Strehle signed the record on 08/18/2015 at 1:15pm, which is before the appointment was scheduled. *Id.* at 31. I additionally note that a separate record documents that Petitioner received his third HPV vaccine on August 17, 2015. *See* Ex. 8 at 2. For these reasons, I find the evidence supports that Petitioner received his third HPV vaccine on August 17, 2015. This finding does not impact my analysis of Petitioner's claim.

[4] On September 28, 2021, a motion to amend the case caption was filed because Mr. Trey Cobb turned 18. ECF No. 69. For the sake of clarity, Mr. Trey Cobb is the Petitioner in this case, and I have referred to him as such throughout this ruling.

Petitioner filed a post-hearing brief on January 5, 2022; Respondent filed his post-hearing brief on April 6, 2022; and Petitioner filed a reply brief on May 6, 2022. ECF Nos. 76, 78, 79. The parties filed a joint status report indicating the record was complete on May 23, 2022. This matter is now ripe for adjudication.

## II. Medical History

Petitioner was in good health prior to his allegedly causal HPV vaccinations. Petitioner received his second HPV vaccination on August 25, 2014 during a routine visit with Dr. Fillman, his primary care physician ("PCP"). Ex. 6 at 16. On August 17, 2015, Petitioner returned to his PCP, where he received his third HPV vaccination. *Id*. at 30. Petitioner was 13- and 14-years old respectively when he received his second and third HPV vaccines.

On October 20, 2015, Petitioner saw Brandon Schreiber, DC, a chiropractor, for mid to lower back pain, headaches, and neck pain, attributed to football. Ex. 7 at 26. Petitioner stated he had been experiencing these symptoms for two weeks and had experienced them "a few times" prior. *Id*. Dr. Schreiber performed a chiropractic evaluation and manipulation. *Id*. at 24-25.

On October 21, 2015, Petitioner presented to Joshua Strehle, DO, at the Guthrie County Hospital. Ex. 6 at 31. He reported that he had been experiencing a sore throat for the past twenty-four hours. *Id*. Dr. Strehle noted that Petitioner's rapid strep test was negative. *Id*. He was advised to call if he developed new symptoms or was not improving within seven days. *Id*.

On November 17, 2015, Petitioner saw Martin Miller, DC, a chiropractor. Ex. 2 at 13. Petitioner reported lower back pain and having "really low energy since school started, feels tired all the time." *Id*. Dr. Miller noted "mildly swollen, tender liver and spleen," and also noted "mono". *Id*. at 14. Petitioner felt relief after chiropractic manipulation, and Dr. Miller advised him to rest until his "liver swelling is decreased." *Id*.

On November 23, 2015, Petitioner followed-up with Dr. Strehle reporting three months of fatigue. Ex. 6 at 33. The medical record noted that over the past two weeks, Petitioner has been unable to complete a full day of school and has begun napping two to three hours each day. *Id.* Some nights he goes to bed as early as 8:00 p.m. and wakes up at 6:30 a.m. *Id*. Petitioner's physical exam was normal. *Id*. Dr. Strehle suggested his fatigue could be secondary to an acute viral illness but noted it didn't explain his ten weeks of fatigue. *Id*. Petitioner's test for infectious mono was negative. *Id*. at 1.

On December 29, 2015, Petitioner presented to Dr. Leona Holcomb, MD, a family medicine doctor, for heat exposure. Ex. 3 at 5-8. Dr. Holcomb noted that Petitioner had been diagnosed with infectious mono in early November and that his history of presentation started in late August. *Id*. His blood test was negative so it was a clinical diagnosis. *Id*. at 5. Petitioner informed Dr. Holcomb that he would fall asleep at 9:00pm and wake up by 7:00am, but would sleep until 9:30am if he is able to. *Id*. He was unable to attend school the whole day, and would have to go home to sleep in the afternoon. *Id*. Petitioner did not feel well rested when he woke up. *Id*. Petitioner had gained 15 pounds in two weeks. *Id*. Dr. Holcomb diagnosed Petitioner with

"chronic fatigue" and a noted family history of liver disease (father with hemochromatosis). *Id.* at 7. Dr. Holcomb believed it was most likely a viral illness, infectious mono as opposed to CMV (cytomegalovirus). *Id.*

On February 11, 2016, Petitioner returned to Dr. Holcomb for his fatigue. Ex. 3 at 9-11. Petitioner informed Dr. Holcomb he had not experienced any relief since being diagnosed. *Id.* at 9. Dr. Holcomb noted "?did have mono—the IGg was + but the IGa was negative." *Id.* Petitioner's self-reported symptoms remained largely the same but Petitioner added that he has issues finding words and has a fainting sensation when he laughs. *Id.* at 9. He is still able to complete his homework. *Id.* Petitioner noted he was more irritable as well. *Id.* at 10. Petitioner also noted that his eyes sometimes twitched, and he could not control the muscles in his face, his speech was delayed and sometimes could not collect his thoughts. *Id.* Dr. Holcomb's assessment was still "chronic fatigue" with "soft neurologic symptoms", and that this "could still be affect [sic] of mono." *Id.* at 11. Dr. Holcomb recommended a neurology consultation. *Id.*

On April 4, 2016, Petitioner visited Dr. Stephen Gutu, MD, a pediatric neurologist, at Blank Children's Hospital Neurology Clinic for fatigue and "facial twitching and muscle weakness since October." Ex. 1 at 1-3. Petitioner's parents informed Dr. Gutu that Petitioner had a "mono-like illness" in late August-September (2015) which resulted in three weeks of extreme fatigue, and Petitioner missed 1.5 weeks of school as a result. *Id.* Petitioner gets 9-12 hours of sleep each night, can fall asleep easily, but wakes frequently and never feels well rested. *Id.* Petitioner also sleeps in the daytime and can fall asleep within one minute of sitting down. *Id.* Petitioner also experiences daily incidents of muscle weakness and "falling" when he laughs or is very excited. *Id.* Petitioner can feel when these incidents will occur and tries to preemptively sit or hold on to something. *Id.* Petitioner denied losing consciousness during these falls. *Id.* Petitioner noted improvement since the peak symptoms in the winter but indicated he still experiences significant effects. Petitioner was referred for a sleep study. *Id.* at 3.

On April 18, 2016, Petitioner was seen for a consultation at the Iowa Clinic by Dr. Gregory Hicklin. Ex. 5 at 19-20. Dr. Hicklin noted that given Petitioner's age and symptoms, he suspected Petitioner suffered from narcolepsy with cataplexy. *Id.* at 19. Dr. Hicklin recommended a polysomnogram[5] and HLA genotype testing. *Id.*

On April 26, 2016, Petitioner underwent a sleep study at West Lakes Sleep Center, which was interpreted by Dr. Hicklin. Ex. 5 at 27-28. In a self-completed sleep questionnaire, Petitioner had an Epworth sleepiness score[6] of 15/24. *Id.* at 27. Petitioner's mean sleep latency time was .50 minutes, indicating a pathological level of daytime sleepiness and his mean REM latency was 1.5

[5] Polysomnogra(phy): the polygraphic recording during sleep of multiple physiologic variables, both directly and indirectly related to the state and stages of sleep, to assess possible biological causes of sleep disorders. https://www.dorlandsonline.com/dorland/definition?id=40298 (last accessed April 20, 2023).

[6] Epworth Sleepiness Scale: a tool for measuring how sleepy a person is during daytime or working hours, using a scale of 1 to 5 for whether the person is unlikely or likely to fall asleep in a series of situations such as watching television, having a quiet conversation, or being stalled in traffic. https://www.dorlandsonline.com/dorland/definition?id=104932 (last accessed March 20, 2023). The scale has a maximum score of 25.

minutes, suggesting narcolepsy. *Id*. at 28. The results of the polysomnogram (PSG)/multiple sleep latency test (MSLT) led to Dr. Hicklin's recommendation for CNS stimulants and avoiding alcohol, sedatives, and using extreme caution when operating a vehicle or machinery. *Id*.

On April 28, 2016, Petitioner followed up with Dr. Hicklin regarding his sleep study results. Ex. 5 at 11-12. Dr. Hicklin's letter stated "He definitely has narcolepsy with cataplexy. His multiple sleep latency test showed sleep onset in less than a minute, and REM sleep seen promptly in all naps, and his nighttime sleep study showed early sleep onset REM. In addition, he gives a great history of cataplexy." *Id*. at 11. Dr. Hicklin noted that Petitioner has "multiple sleep problems. Obviously he has narcolepsy with cataplexy but he also has the fragmented sleep that may be seen with narcolepsy and obstructive sleep apnea" so he recommended tackling the narcolepsy with cataplexy first. *Id*. at 12. Dr. Hicklin prescribed methylphenidate and fluoxetine for Petitioner's narcolepsy and talked to Petitioner's school nurse about nap therapy during school hours. *Id*.

On June 10, 2016, Petitioner returned to Dr. Gutu for a follow up. Ex. 1 at 5-7. Dr. Gutu noted Petitioner's history of present illness (HPI) was narcolepsy/cataplexy but other differential diagnoses in April 2016 were possible complications from post mononucleosis fatigue syndrome. *Id*. at 5. Dr. Gutu noted that Petitioner had a PSG and MSLT which were diagnostic of narcolepsy. *Id*. Dr. Gutu recommended HLA DQB1 testing and that he continue with his medications.[7] *Id*. at 7. Dr. Gutu referred Petitioner to Dr. Steven Zorn at the Iowa Sleep Disorders Center. *Id*.

Petitioner returned to Dr. Hicklin on June 20, 2016 for a follow up. Petitioner informed Dr. Hicklin that the medications had helped him significantly; he sleeps well at night and has strategic naps to feel more rested and alert. Ex. 5 at 6-7. Petitioner reported he still had episodes of cataplexy. *Id*. at 6. Dr. Hicklin increased Petitioner's fluoxetine dosage and recommended he get an accommodation at school. *Id*. at 7. Dr. Hicklin recommended Petitioner follow up with his neurologist, Dr. Gutu.

On June 27, 2016, Petitioner visited Dr. Steven Zorn at the Iowa Sleep Disorders Clinic. Ex. 4 at 6-9. Dr. Zorn noted that his Epworth score was 16. *Id*. at 6.

On July 25, 2016, Dr. Zorn followed up with Petitioner after another PSG, which was negative for obstructive sleep apnea (OSA). Ex. 4 at 10-12. Dr. Zorn did not believe Petitioner had a secondary sleep problem. *Id*. at 10.

On August 5, 2016, Petitioner returned for another appointment with Dr. Zorn. Ex. 4 at 13-15. Petitioner's Epworth score was 12 and it was noted he was not experiencing side effects from Concerta and that his dosage should be increased. *Id*. at 15.

On August 18, 2016, Petitioner returned to Iowa Sleep Disorders Center for another follow up with Dr. Zorn. Ex. 4 at 16-18. Petitioner reported that his narcolepsy was under control and he

[7] It is unclear from the medical records filed if Petitioner ever received genetic testing for the HLA DBQ1 gene.

felt improved. *Id*. at 16. Petitioner also reported that he was not experiencing issues with his stimulant medications. *Id*. Petitioner's Epworth score was now 9. *Id*. at 18.

Petitioner's last appointment with Dr. Zorn was on February 16, 2017. Ex. 4 at 19-21. Petitioner had no medication side effects and Dr. Zorn recommended adding Xyrem for his cataplexy. *Id*. at 19. Petitioner declined. *Id*.

No other relevant medical records were submitted.

## III. Affidavit and Fact Testimony

### A. Affidavit of Kimberly Cobb, Petitioner's Mother

Petitioner filed an affidavit signed by Mrs. Kimberly Cobb on December 15, 2017. Ex. 10. In it, she stated that her son was a normal teenager before his third HPV vaccine. *Id*. at 2. She further averred that she believes the HPV vaccine caused her son to develop narcolepsy and cataplexy. *Id*. Since the vaccination, Petitioner has been unable to engage in his normal activities without taking medication. *Id*. He continues to suffer from narcolepsy and cataplexy, which has caused him to experience "extreme fatigue, inconsistent sleeping patterns, irritability and fear of collapse after excitement, restlessness, and muscle weakness." *Id*. at 3.

### B. Petitioner's Testimony

Petitioner testified at the entitlement hearing on September 21, 2021. At the time of the entitlement hearing, Petitioner was a 20-year old junior at the University of Iowa, majoring in actuarial sciences. Tr. at 5. Petitioner's symptoms began during the 2015-2016 school year, when he was a high school freshman. *Id*. at 6. After receiving his third HPV vaccine, Petitioner began feeling tired, and would fall asleep during almost every class, every day towards the beginning of September 2015. *Id*. at 6-7. Petitioner also experienced cataplexy attacks, where he would laugh, fall over, and have no control over his body. *Id*. at 7. Something that would elicit strong emotions would trigger his cataplexy. *Id*. Petitioner's words would slur, face would droop, eyes would close, and head would bob. *Id*. Petitioner's narcolepsy with cataplexy affected his social life; he would fall asleep while standing up at football and basketball practice. *Id*. at 8. Whenever he attended social events, he would fall asleep before others; eventually he stopped going to and being invited to events with his friends, since he couldn't participate. *Id*.

Petitioner testified that he first received his diagnosis around April 2016 and had completed most of the school year without knowing his condition. Tr. at 8-9. Petitioner admitted he didn't know what to think at first but it was tough to learn it would never go away. *Id*. at 9. His family, especially his mother, was devastated. *Id*. Petitioner's friends were shocked because they thought his cataplexy attacks were just him messing around. *Id*.

Petitioner now has to structure his days and weeks around his narcolepsy. Tr. at 10. If he doesn't, he can't get any work done. *Id*. Petitioner has a strict sleep schedule and limited social life. *Id*. Petitioner testified that he does not have the energy to do things a typical college student does. *Id*. His major is quite demanding and as a result, does not allow him to do much else in terms

of intramurals or clubs, because they generally happen at night and he has to sleep at that time. *Id.* Petitioner testified that he begins to wind down around 7:00pm every night because he is tired. *Id.* Petitioner also does not drive more than 15 minutes without caffeine or medications or both because he does not trust himself. *Id.* at 10-11.

Petitioner regulates his cataplexy attacks with Xyrem. Tr. at 11. He once went on a trip where he did not take his medication for three to four days and had attacks ten times per day on the trip. *Id.*

Petitioner testified that his routine involves going to bed around 10:00pm. Tr. at 12. He goes to bed as late as he can because Xyrem lasts for 2.5-3 hours, so he wakes up during the night to take two doses of Xyrem and tries to go back asleep. *Id.* He wakes up around 4:00am and tries to go back to sleep until 5:45am. *Id.* Petitioner then takes "a decent amount of caffeine" prior to going to the gym and then returns home to sleep another 30 minutes. *Id.* Petitioner takes methylphenidate (Ritalin) and drinks coffee before going to class. *Id.* at 12-13. Petitioner will stay awake during his 8:30am class but will usually fall asleep during his 10:30am class. *Id.* at 13. He will nap around lunch, go to his afternoon class and fall asleep a few times in that class. *Id.*

Petitioner used to take more medications in high school but did not enjoy the side effects, including increased heart rate. Tr. at 13-14. He now regulates his symptoms through diet and sleep. *Id.* at 14. Petitioner can get about two hours of work done before his "brain kind of turns off." *Id.* Petitioner also testified that his cataplexy can occur at any time, including when he's driving. *Id.* at 16.

Lastly, Petitioner attributed some weight gain to his condition. Tr. at 16. Petitioner was always skinny, but gained 20 pounds in about two weeks his freshman year (during football season). *Id.* at 17. Xyrem has helped him lose the weight he had gained. *Id.* Petitioner's mood is also affected by his condition; he is often short tempered when tired. *Id.* When Petitioner meets new people, others think he is unfriendly or unenergetic or that he is using drugs because his eyes are droopy and he looks tired. *Id.* It is a lot of effort and energy for Petitioner to smile all the time. *Id.* Petitioner would not be able to function normally without his medication, and would not be able to sleep at night. *Id.* at 18.

## IV. Expert Opinions and Qualifications

### A. Dr. Lawrence Steinman

#### 1. Qualifications

Dr. Steinman received his medical degree from Harvard University in 1973 and completed his residency at Stanford University in pediatrics and pediatric and adult neurology. Steinman CV at 1. Dr. Steinman is board certified in neurology. *Id.* at 2. He has taught neurology, pediatrics, and genetics since 1980 and is currently a professor at Stanford University in the departments of Neurology, Pediatrics, and Genetics; he is also the George A. Zimmermann Professor of Neurological Sciences at Stanford University. *Id.* at 1. Dr. Steinman has approximately 50 patents and has published approximately 600 peer-reviewed papers. *Id.* at 2-46; Tr. at 20, 26. Dr. Steinman

has published 10 papers specific to the topic of narcolepsy. Tr. at 19-20, 23. He also treats patients with neuroimmunological diseases and approximates he has treated thousands of such patients over the course of his career. *Id.* at 27. I recognized him as an expert in neurology, neuroimmunology, and immunology. *Id.*

2. Expert Reports

Dr. Steinman authored two expert reports. Exs. 11 ("First Steinman Rep."); 43 ("Second Steinman Rep.").

a. First Expert Report

In his first expert report, Dr. Steinman opined that Petitioner's narcolepsy with cataplexy was caused by the August 2015, or third dose of the HPV vaccine. First Steinman Rep. at 1, 27. Dr. Steinman theorized that the components of the "HPV vaccine contain molecular mimics of hypocretin, also called orexin," and that "[t]he HPV vaccine also contains mimics of the hypocretin-2 receptor, also known as the orexin-2 receptor." *Id.* at 7. Dr. Steinman opined that the mechanism of molecular mimicry caused Petitioner's immune system to attack the cells in his brain that produce hypocretin and that the resulting hypocretin deficiency caused him to develop narcolepsy. *Id.* at 9.

Prior to delving into the crux of his molecular mimicry theory, Dr. Steinman discussed the potency of the HPV vaccine. First Steinman Rep. at 9. He cited to the Souayah paper to support his position that the HPV vaccine elicits an abnormally strong immune response. Dr. Steinman stated that, "Gardasil elicits a stronger immune response than the natural viral infection. There is a 40-fold increase in HPV antibodies as compared to what is seen in natural HPV infection." *Id.* (citing Souayah et al., *Guillain-Barre Syndrome After Gardasil Vaccination: Date from Vaccine Adverse Event Reporting System,* 2006-2009, 29 VACCINE 886-889 (2011) (filed as Ex. 21) (hereinafter "Souayah")).

To support his theory of causation, Dr. Steinman noted that molecular mimicry "can trigger clinical neuroinflammatory disease in a susceptible individual if the mimicry is directed to a 'disease causing' epitope." First Steinman Rep. at 9. Based on his own research, Dr. Steinman opined that his "criterion for a 'meaningful molecular mimic'" is that the self-antigen and foreign antigen share a sequence of at least five amino acids out of 12, or at least four out of 11. *Id.* at 10. Moreover, the matching amino acids need not be consecutive. *Id.* (citing to Gautam et al., *A polyalanine peptide containing only five native myeline basic protein residues induces autoimmune encephalomyelitis*, 127 JOURNAL OF EXPERIMENTAL MEDICINE 605-609 (1992) (filed as Ex. 32; (hereinafter "Gautam 1"); Gautam et al., *Minimum structural requirements for peptide presentation by major histocompability complex class II molecules: Implications in induction of autoimmunity*, 161 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, 767-771 (1994) (filed as Ex. 33; hereinafter "Gautam 2"); Gautam et al., *A viral peptide with limited homology to a self-peptide can induce clinical sign of experimental autoimmune encephalomyelitis*, 161 JOURNAL OF IMMUNOLOGY, 60-64 (1998) (filed as Ex. 34; hereinafter "Gautam 3")).

Using the web-based Basic Local Alignment Search Tool ("BLAST"), Dr. Steinman compared the amino acid sequence structure of hypocretin and the brain's hypocretin receptors with the HPV 6, 11, 16, 18 L1 proteins in the HPV vaccine. First Steinman Rep. at 13-21. Based on the BLAST search results, Dr. Steinman opined that there is homology between hypocretin and hypocretin receptors (HRCT-R2) and components of the vaccine that is sufficient to cause clinically relevant neuroinflammation. *Id.* at 13, 14, 17, 19, 21.

Dr. Steinman stated that he developed his theory of causation based in part on the results of a study in which laboratory mice were implanted with "cells that were primed with the papilloma virus peptide," all of whom developed severe relapsing-remitting experimental autoimmune encephalomyelitis ("EAE"). First Steinman Rep. at 21 (citing Ufret-Vincenty, et al., *In Vivo Survival of Viral Antigen-specific T Cells that Induce Experimental Autoimmune Encephalomyelitis*, 188 JOURNAL OF EXPERIMENTAL MEDICINE, 1725-1738 (1998) (filed as Ex. 36). Dr. Steinman acknowledged that the use of adjuvants in this study drastically increased the incidence of EAE in the test group, but he nevertheless found the results compelling. *Id.*

Dr. Steinman acknowledged that, for several reasons, it is not possible to test Petitioner for immunity for the HPV molecular mimics. First Steinman Rep. at 22. He noted that such a test would constitute medical research requiring ethical review and substantial funding. *Id.*

Dr. Steinman opined that "immunity to nervous system antigens like myelin is rather widespread in normal individuals." First Steinman Rep. at 24. He continued, saying that "immunity to myelin is necessary but not sufficient" for development of an autoimmune disease. *Id.* Dr. Steinman added that most people with immunity to nervous system antigens do not develop autoimmune diseases because "[o]ther genetic and environmental factors are necessary before these self-reactive immune responses to myelin for example, or to orexin and HCRT-R2 might trigger inflammation in the brain." *Id.* Dr. Steinman argued that the medical literature suggesting that the HPV vaccine elicits a stronger immune response than a natural infection supports his theory that the HPV vaccine caused Petitioner's narcolepsy. *Id.*

Dr. Steinman cited to a cohort study of adolescent girls in which the authors found that the incidence of narcolepsy among those who had received the HPV vaccine was 2.61 per 100,000, as opposed to an incidence of 1.81 per 100,000 among unvaccinated subjects. First Steinman Rep. at 26 (citing Arnheim-Dahlstrom, et al., *Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study*, 347 BRITISH MEDICAL JOURNAL f9506 (2013) (filed as Ex. 40) (hereinafter "Arnheim-Dahlstrom"). Dr. Steinman conceded that the difference between the two groups did not rise to the level of statistical significance, but nevertheless found the result persuasive due to the large sample size (230,018 subjects). *Id.*

Dr. Steinman opined that the timing of the diagnosis of Petitioner's narcolepsy (April 2016, approximately nine months after receiving the third dose) is consistent with the medical literature on vaccines and narcolepsy. First Steinman Rep. at 27. For example, a Finnish study linked the Pandemrix vaccine to a 12.7-fold increase in the risk of developing narcolepsy within eight months of vaccination. *Id.* (citing Partinen, et al., *Increased Incidence of Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland*, 7 PLoS ONE 3

(2012) (filed as Ex. 41). A British study found a similar elevated risk, with onset occurring from three to 14 months after vaccination. *Id.* (citing Winstone et al., *Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England*, 56 DEV. MED. CHILD NEUROL. 1117-23 (2014) (filed as Ex. 42)).

b. Second Expert Report

In his second expert report, Dr. Steinman first responded to comments from Dr. Brown. Second Steinman Rep. at 1. Dr. Steinman indicated that he agrees with Dr. Brown's diagnosis of "narcolepsy with cataplexy which presented at a typical age." *Id.* Dr. Steinman likewise agreed with Dr. Brown's statement that he strongly recommends that his patients, including those with narcolepsy, receive all vaccines, including HPV. *Id.* Dr. Steinman noted that the recommendation to administer or withhold a vaccine is based on weighing the risks and benefits for that individual person, and that rare adverse events sometimes occur. *Id.* at 2.

Dr. Steinman went on to reprise his analysis of the BLAST results from his first expert report. Second Steinman Rep. at 2. Dr. Steinman opined that the comparison of the amino acid chains in hypocretin with the HPV 11 L1 protein found in the HPV vaccine have yielded new insight. *Id.* at 2-3. Having found in his first report that this comparison revealed a "degree of homology sufficient to induce clinical[ly] relevant neuroinflammation," Dr. Steinman cited to medical literature where the hypocretin epitope in question "was identified as being a target or cytotoxic T cells found in the cerebrospinal fluid in patients with Type 1 narcolepsy." *Id.* at 3, 5. (citing Latorre et al., *T cells in patients with narcolepsy target self-antigens of hypocretin neurons*, 562 NATURE 62-68 (2018) (filed as Ex. 44) (hereinafter "Latorre"). Dr. Steinman opined that the data "dramatically bolster" Petitioner's theory of causation, and that "this is about as close to discovering a 'smoking gun' in a vaccine as modern science can currently provide." *Id.* at 6.

The Latorre study used two different methods "to interrogate the T cell repertoire of patients with narcolepsy." Latorre at 1. The authors stated that "[t]he findings of [their] study demonstrate the existence, in patients with narcolepsy, of autoreactive CD4+ and—in some cases—CD8+ T cells that target self-antigens expressed by neurons that produce [hypocretin]." *Id.* at 5. They stated that "[t]he findings of autoreactive CD4+ and CD8+ T cells in narcolepsy raises questions as to their possible pathogenic role." *Id.* at 5.

Dr. Steinman next described an enhanced search process that he used to identify molecular mimics between the HPV vaccine and the self-antigens that are targeted in narcolepsy. Second Steinman Rep. at 6-11. He reiterated and emphasized his opinion that there is sufficient homology between the two to say that the HPV vaccine could have caused Petitioner's narcolepsy by way of molecular mimicry. *Id.*

Finally, Dr. Steinman disagreed with Dr. Fujinami's opinion that the use of altered peptide ligands in the HPV vaccine makes it more likely than not that the HPV vaccine "would favor protection against autoimmune disease/narcolepsy rather than inducing narcolepsy." Second Steinman Rep. at 10 (citing Fujinami Rep. at 3). He argued that, instead, "the known experience in humans is that altered peptides can exacerbate disease when injected into a human." *Id.* (citing Bielekova et al., *Encephalitogenic potential of myelin basic protein peptide (amino acids 83-99)*

*in multiple sclerosis: Results of a phase II clinical trial with an altered peptide ligand*, 6 NATURE MED. 10, 1167-75 (2000) (filed as Ex. 45) (hereinafter "Bielekova"); Genain and Zamvil, *Specific immunotherapy: One size does not fit all*, 6 NATURE MED. 10, 1098-1100 (2000) (filed as Ex. 46); Kappos et al., *Induction on a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial*, 6 NATURE MED. 10, 1176-82 (2000) (filed as Ex. 47) (hereinafter "Kappos").

3. Testimony

During the entitlement hearing on September 21, 2021, Dr. Steinman described his process for conducting BLAST searches and the results that he received. Tr. at 29-30. He indicated that he conducts BLAST searches when asked to provide an expert opinion in a case and that if the results do not show sufficient homology between the vaccine and a self-antigen, he declines the case. *Id.* at 29. Dr. Steinman identified a paper published in Nature a few months after his first expert report, in which one of the parts of orexin was attacked by the immune system of people with narcolepsy. *Id.* at 31. Dr. Steinman testified that his BLAST results revealing the homologies between orexin and the HPV vaccine components was "inescapably associated with autoimmunity and narcolepsy." *Id.* He further testified that BLAST is commonly accepted in the medical community as a way of identifying potential immune system targets. *Id.* at 44-45.

Dr. Steinman responded to Dr. Fujinami's reliance on medical literature suggesting that altered peptide ligands may actually reduce the chance of an autoimmune reaction. Tr. at 60-66. Dr. Steinman opined that, while initially promising in laboratory animals, three studies involving altered peptide ligands did not yield good results in humans. *Id.* (citing Ruiz et al., *Microbial Epitopes Act as Altered Peptide Ligands to Prevent Experimental Autoimmune Encephalomyelitis*, 189 J. EXP. MED. 8 1275-83 (1999) (filed as Ex. C, Tab 4); Bielekova, et al.; Kappos, et al.). In fact, Dr. Steinman noted that two of the trials were discontinued because of allergic reactions to the altered peptide in human subjects. *Id.* at 63-64.

Dr. Steinman opined that, based on the medical record, the onset of Petitioner's narcolepsy occurred two to three weeks after he received the third dose of the HPV vaccine. Tr. at 68-69. Dr. Steinman went on to opine that, while detailed data on the timing of narcolepsy onset after vaccination is not available, two to three weeks is "typical of an autoimmune reaction causing a neuroinflammatory condition." *Id.* at 69-70.

The Respondent elected not to ask Dr. Steinman any questions on cross examination during the Petitioner's case-in-chief or during rebuttal. Tr. at 75, 163.

**B. Dr. Lawrence Brown**

1. Qualifications

Dr. Brown received his medical degree from New York University in 1971. Ex. B ("Brown CV") at 1. Until his retirement in July 2021, he held the position of Associate Professor of Neurology and Pediatrics at the University of Pennsylvania School of Medicine and was co-

director of the Pediatric Neuropsychiatry Center at the Children's Hospital of Philadelphia. *Id.* at 2; Tr. at 146. He is board certified in pediatrics and neurology with special competence in pediatric neurology and sleep medicine. Brown CV at 2. Dr. Brown's research focuses on sleep disorders and other neurological conditions in children and infants. *Id*. at 10-11. He has co-authored nearly 40 peer-reviewed journal articles, 36 book chapters and reviews, and has been an associate editor of all four editions of the *Clinical Handbook of Pediatrics*. *Id*. at 10-14. I recognized Dr. Brown as an expert in neurology. Tr. at 147-48.

2. Expert Report

Dr. Brown authored one expert report. Ex. A (hereinafter "Brown Rep."). Dr. Brown provided a detailed clinical description of narcolepsy, including the typical presentation, causes, diagnostic criteria, and treatment modalities. Brown Rep. at 2-5.

Dr. Brown agreed with the diagnosis of narcolepsy with cataplexy. Brown Rep. at 6. Dr. Brown acknowledged that narcolepsy has been associated with the Pandemrix flu vaccine, "but this was only true in a single situation." *Id*. at 5. He stated that "[i]t remains unclear whether the increase in incidence of narcolepsy in 2009 to 2010 was related to an antigen contained in the vaccine, the influenza vaccination itself, or to both." *Id*. (citations omitted). Dr. Brown emphasized his opinion that the Pandemrix situation was unique and noted that other flu vaccines formulated over the past few years had not caused an increase in narcolepsy. *Id*. at 5-6. Dr. Brown opined that "[t]here is no reported association of HPV vaccines and narcolepsy" and there is no question that Trey Cobb has a diagnosis of narcolepsy with cataplexy which presented at a typical age. *Id.* Specifically, Dr. Brown states,

> While it is true that he had a third Gardasil vaccination about the time that he first developed symptoms, there is no scientific support that would suggest that this was anything but an unrelated coincidence. I understand that narcolepsy type 1 is most likely an autoimmune disorder targeting orexin containing neurons in the hypothalamus. Molecular mimicry has been hypothesized to be the cause of the regional epidemic of narcolepsy caused by the Pandemrix flu vaccine in 2009-2010, this has never been demonstrated in other flu vaccines or, more to the point, in HPV vaccines.

Brown Rep. at 6. Finally, Dr. Brown concluded, "I feel strongly that Trey Cobb suffers from idiopathic narcolepsy type 1 which has no direct or indirect association with administration of the HPV vaccine." *Id*.

3. Testimony

During the entitlement hearing on September 21, 2021, Dr. Brown reiterated his opinion that Petitioner's medical record meets the clinical criteria for narcolepsy with cataplexy. Tr. at 152. Dr. Brown expressed a lack of certainty as to the timing of onset of Petitioner's narcolepsy but agreed that the medical record shows no evidence of cataplexy prior to Petitioner's third dose of the HPV vaccine. *Id*. at 152-53. Dr. Brown opined that nearly all narcolepsy cases are idiopathic, meaning that there is "no clear etiology for what causes the loss of orexin receptors in that part of

the hypothalamus." *Id.* at 155. Dr. Brown also stated that there were reasons to believe autoimmunity is involved but the HLA genotype was also commonly associated with type 1 narcolepsy. *Id.* at 148. Daytime sleepiness is common, particularly amongst teenagers, and one of those reasons is narcolepsy. *Id.* at 148-49. Among common type 1 narcolepsy symptoms is weight gain and irritability. *Id.* at 149. Dr. Brown also reiterated his opinion that "there is little evidence that [the] HPV vaccine causes narcolepsy," based on the Torstensen article. *Id.* at 150; Torstensen et al., *Type 1 narcolepsy is not present in 29 HPV-vaccinated individuals with subjective sleep complaints*, 68 DANISH MEDICAL JOURNAL 1-4 (2018) (filed as Exs. A, Tab 19 and C, Tab 6) (hereinafter "Torstensen"). The study included half a million women and within the 700 women with significant complaints, 27 had sleep complaints but none fulfilled the clinical criteria for narcolepsy. *Id.* Between the Torstensen study and the Red Book of Immunizations from the Academy of Pediatrics, Dr. Brown asserted he did not believe there was any increased serious risk that the HPV vaccine causes narcolepsy. *Id.*

**C. Robert S. Fujinami, Ph.D.**

1. Qualifications

Dr. Fujinami received his Ph.D. in immunology and microbiology from Northwestern University in 1977. Ex. D ("Fujinami CV") at 1. Since 2007, he has held two positions within the University of Utah School of Medicine, Professor in the Department of Pathology and Adjunct Professor in the Department of Neurology. *Id.* Dr. Fujinami is the author of more than 150 peer-reviewed journal articles. *Id.* at 20-50. His research focuses on neuroinflammation in the context of central nervous system autoimmune diseases and the role of infections in initiating seizures leading to epilepsy. First Fujinami Rep. at 1. Dr. Fujinami has published extensively on the topic of molecular mimicry and autoimmunity. *See generally* Fujinami CV at 20-50. He is a professor in the department of pathology at the University of Utah; he serves as vice dean for faculty, and assistant vice president of academic affairs for University of Utah Health. Tr. at 78-79. I recognized Dr. Fujinami as an expert in immunology. Tr. at 81.

2. Expert Reports

Dr. Fujinami authored two expert reports in this matter. Exs. C (hereinafter "First Fujinami Rep."); E (hereinafter "Second Fujinami Rep.").

a. First Expert Report

In his first expert report, Dr. Fujinami disagreed with Dr. Steinman's theory that the HPV vaccine caused Petitioner's narcolepsy by means of molecular mimicry. First Fujinami Rep. at 2. Dr. Fujinami criticized Dr. Steinman's citation of medical literature in which researchers induced development of experimental autoimmune encephalomyelitis ("EAE") in laboratory animals. *Id.* Dr. Fujinami pointed out that this study involved an injection of peptides in a powerful adjuvant such as Freund's adjuvant as opposed to the aluminum adjuvant in the HPV vaccine. *Id.* Dr. Fujinami opined that other studies have found that laboratory animals injected with whole myelin with an aluminum adjuvant did not develop EAE. *Id.* (citing Sicotte et al., *Immunization with myelin or recombinant Nogo-66/MAG in alum promotes axon regeneration and sprouting after*

*corticospinal tract lesions in spinal cord*, 23 MOLECULAR AND CELLULAR NEUROSCIENCE 251-63 (2003) (hereinafter Sicotte); Wallberg et al., *Vaccination with myelin oligodendrocyte glycoprotein adsorbed to alum effectively protects DBA/1 mice from experimental autoimmune encephalomyelitis*, 33 EUROPEAN JOURNAL OF IMMUNOLOGY 1539-47 (2003) (hereinafter "Wallberg"). He stated further research has suggested that laboratory animals injected with a protein often used to induce EAE with an aluminum adjuvant "were actually protected from autoimmune neuroinflammatory disease." *Id*. at 3. Dr. Fujinami opined that these data support his contention that "if there were molecular mimicry with 'disease-relevant' immunologic epitope(s) contained in the HPV vaccine cross-reacting…with orexin/hypocretin or HCRT-R2 epitopes, then it would not induce neural autoimmune disease." *Id*. (emphasis in original).

In response to Dr. Steinman's analysis of the BLAST results showing similarity between the HPV L1 protein from the vaccine and hypocretin and HCRT-R2, Dr. Fujinami opined that "we do not know if these autoantibodies are pathogenic for narcolepsy." First Fujinami Rep. at 3.

Dr. Fujinami further opined that Dr. Steinman's own research on altered peptide ligands supported Dr. Fujinami's criticism of Dr. Steinman's theory of causation. First Fujinami Rep. at 3. Dr. Fujinami noted that "suppression of autoimmune disease is more likely than not to occur if there were actual 'disease-relevant' mimicking peptides in the alum-based HPV vaccine with cross-reactivity to orexin/hypocretin or HCRT-R2." *Id*.

Dr. Fujinami stated that there is no association between HPV vaccination and development of narcolepsy. First Fujinami Rep. at 3. Dr. Fujinami acknowledged that one batch of the influenza vaccine Pandemrix that was administered in Sweden was associated with increased cases of narcolepsy. *Id*. He cited to studies conducted after the Swedish narcolepsy cases by various entities, including the CDC and WHO, which found no link between the HPV vaccine and narcolepsy. *Id*. (citing Torstensen, et al.). Dr. Fujinami also noted that the authors of a large cohort study found "'no evidence supporting associations between exposure to qHPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events.'" *Id*. at 4 (quoting Arnheim-Dahlstrom, et al.).

Dr. Fujinami concluded by reiterating his opinion that "the HPV vaccination(s) the Petitioner received did not cause his narcolepsy." First Fujinami Rep. at 4.

b. Second Expert Report

In his second expert report, Dr. Fujinami disagreed with Dr. Steinman's contention that the article by Latorre bolsters Dr. Steinman's theory of causation. Second Fujinami Rep. at 1 (citing Second Steinman Rep. at 3). Dr. Fujinami pointed out the authors state that their 'results do not support a molecular mimicry between HCRT (hypocretin) and TRIB2 antigens and influenza virus, and raise questions as to the role of HLA-DQB1*06:02 in antigen presentation." *Id*. (quoting Latorre, et al.). Dr. Fujinami opined that the conclusion in the La Torre article actually "runs counter to Dr. Steinman's proposed molecular mimicry theory where the 'mimicking' hypocretin epitope found in the HPV and influenza vaccines causes narcolepsy through the mimicry mechanism." *Id*.

Dr. Fujinami also reiterated his position that "altered peptide ligands in weak adjuvants such as alum could be used to protect animals against disease." Second Fujinami Rep. at 1. He disagreed with Dr. Steinman's reliance on two articles in which patients with multiple sclerosis were injected with whole myelin. *Id.* at 1-2 (citing Bielekov, et al.; Kappos, et al.). Dr. Fujinami pointed out that these authors were analyzing a new treatment protocol in patients who had an ongoing disease, which he noted is "very different than treating individuals before the occurrence of the disease and demonstrating protection." *Id.* at 2. He also asserted that his original point was "that immunizing individuals who do not have narcolepsy or MS with mimicking peptides in alum would not induce disease." *Id.* Dr. Fujinami further opined that "treating relapsing-remitting MS patients with peptide mimics did not make the disease worse," which, he asserted, does not support Dr. Steinman's theory of causation. *Id.*

Dr. Fujinami concluded by reiterating his opinion that "molecular mimicry is not a likely mechanism for vaccination causing narcolepsy in the Petitioner." Second Fujinami Rep. at 2.

3. Testimony

During the entitlement hearing on September 21, 2021, Dr. Fujinami opined that the type of adjuvant used in a vaccine determines the strength of the immune response. Tr. at 89. He went on to cite his own work on molecular mimicry, testifying that, in order for the immune response to be robust enough for molecular mimicry to cause disease, a vaccine must contain a powerful adjuvant such as complete Freund's adjuvant. *Id.* at 90. Dr. Fujinami opined that, by contrast, there is evidence that weak adjuvants such as alum and incomplete Freund's adjuvant offer some protection from autoimmune disease. *Id.* at 92, 94.

Dr. Fujinami also disagreed with Dr. Steinman's criticism of his altered peptide ligand literature. Tr. at 100. Dr. Fujinami noted that the trials in which human subjects did not tolerate the altered peptides well are not comparable to Petitioner's situation. *Id.* at 100-01. Dr. Fujinami noted that the patients in those studies already had full-blown multiple sclerosis, and thus were not comparable to a patient like Petitioner who did not have an autoimmune disorder. *Id.* at 101.

Dr. Fujinami restated his opinion that, based on the medical literature, there is no association between the HPV vaccine and narcolepsy. Tr. at 107-09 (citing Arnheim-Dahlstrom at 5). He referenced Arnheim-Dahlstrom, who observed no significant association between the HPV vaccine and narcolepsy, and noted his agreement with that study. *Id.* at 108.

## V. Applicable Law

### A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, when a petitioner suffers an alleged injury that is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

In attempting to establish entitlement to a Vaccine Program award of compensation for a off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit

in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Under the first prong of *Althen*, a petitioner must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner's burden. *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359-60 (Fed. Cir. 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). However, special masters are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Boatmon*, 941 F.3d at 1360, *quoting Moberly*, 592 F.3d at 1324. Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Hock v. Sec'y of Health & Hum. Servs.*, No. 17-168V, 2020 U.S. Claims LEXIS 2202 at *52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

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

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011),

*aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id*. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem*., 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

**B. Law Governing Analysis of Fact Evidence**

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs*., 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL

6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd, Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

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

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

### C. Analysis of Expert Testimony

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

technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted").

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations").

### D. Consideration of Medical Literature

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

## VI. Analysis

Because Petitioner does not allege an injury listed on the Vaccine Injury Table, his claim is classified as "off-Table." As noted above, to prevail on an "off-Table" claim, Petitioner must prove by preponderant evidence that he suffered an injury and that this injury was caused by the vaccination at issue. *See Capizzano*, 440 F.3d at 1320.

Although the petition pleads a significant aggravation claim, both parties have agreed that Petitioner's narcolepsy symptoms began after third HPV vaccination. *See* Pet'r's Post-Hearing Brief at 1 ("This lack of orexin caused daytime sleepiness, significant weight gain, and a sudden

loss of muscle tone (cataplexy) shortly after Trey receive at the third Gardasil vaccine on August 17, 2015"); *see also* First Steinman Rep. at 27 ("To a reasonable degree of medical certainty, by a preponderance of the evidence, the Petitioner developed narcolepsy with cataplexy from the Gardasil immunization in August 2015). Accordingly, I have analyzed this case pursuant to *Althen v. Secretary of Health and Human Services*.

### A. Narcolepsy and Cataplexy Generally

Narcolepsy is a chronic neurological disorder, characterized by excessive and irresistible sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Brown Rep. at 2. Excessive daytime sleepiness ("EDS") is a core clinical feature of narcolepsy that presents in both children and adults. *Id*. Narcolepsy is a lifelong condition, which typically begins in childhood or early adulthood "with a peak in mid-adolescence." *Id*. Narcolepsy is not a common disorder, appearing in 1:2000 to 1:5000 of the population. *Id*.

Narcolepsy has two classifications: type 1 (narcolepsy with cataplexy) and type 2 (narcolepsy without cataplexy). Brown Rep. at 2. According to Dr. Brown, "clinicopathologic studies involving patients with narcolepsy type 1 demonstrate selective loss of orexin-secreting neurons in the hypothalamus and little or no detectable orexin[8] in cerebrospinal fluid." *Id*. at 3. Genetic factors also play an "important role" in the predisposition for narcolepsy. *Id*. The HLA DQB1-0602 gene has been found to be strongly supportive of a narcolepsy diagnosis but not routinely tested. *Id*. at 4. Narcolepsy is diagnosed with polysomnography but can also be confirmed with a lumbar puncture measuring orexin levels. *Id*.

"Cataplexy is characterized by sudden, transient loss of muscle tone", which typically occurs as a response to "strong emotions such as laughter, surprise, anger, fright, or anticipation of reward." Brown Rep. at 3. The severity of cataplexic attacks ranges from "a slight head or shoulder drop to a sudden collapse to the floor." *Id*.

### B. Petitioner Has Carried His Burden of Proof

I have discussed the *Althen* prongs in the order of their significance to the case.

#### 1. *Althen* Prong One

In the context of the Program, "to establish causation, the standard of proof is preponderance of evidence, not scientific certainty." *Langland v. Sec'y of Health & Hum. Serv.*, 109 Fed. Cl. 421, 441 (2013). Petitioner's burden under *Althen*'s first prong is to provide a medical theory causally connecting the vaccination and the injury. *Id*. This theory must be sound and reliable. *Boatmon*, 941 F.3d at 1359.

[8] Various medical articles refer to orexin and hypocretin interchangeably. For ease of reference, I have consistently referred to the neuropeptide as orexin.

a. Dr. Steinman's Theory[9]

Humans have a limited number of neurons that produce orexin. Orexin is a neuropeptide that regulates appetite and wakefulness. Tr. at 35. A substantial enough decrease in orexin-producing neurons leads to the development of narcolepsy. *Id.* at 84; Latorre at 63; NIH, National Institute of Neurological Disorders and Stroke, Narcolepsy Fact Sheet, 1-10, 3 (filed as Ex. 48) (hereinafter "Narcolepsy Fact Sheet"). Type 1 narcolepsy is generally considered to be an autoimmune condition whose pathogenesis likely involves an immune response to orexin. Tr. at 36; Narcolepsy Fact Sheet at 3-4; Brown Rep. at 6 (stating that "narcolepsy type 1 is most likely an autoimmune disorder targeting orexin containing neurons in the hypothalamus."). Dr. Steinman contends there is homology between components of orexin and the L protein portion of the Gardasil vaccine. According to Dr. Steinman, this homology can result in a cross-reactive immune response which causes the destruction of neurons that produce orexin and eventually leads to narcolepsy.

*i. Step 1: BLAST Search*

BLAST, or Basic Local Alignment Search Tool, is a program that "finds regions of similarity between biological sequences." NIH, National Library of Medicine, BLAST; blast.ncbi.nlm.nih.gov/Blast.cgi; Tr. at 28-29. Dr. Steinman, through a BLAST search, identified homologies, or what Dr. Steinman believes are "meaningful molecular mimics," between the Gardasil vaccine and orexin, thus linking the vaccine to narcolepsy. First Steinman Rep. at 10-21. Dr. Steinman defined a "meaningful molecular mimic" as "a run of 5 or more of 12 amino acids that are identical." *Id.* at 10.

Dr. Steinman bases his position that five or more identical amino acids will produce disease on three papers. These papers, each authored by Gautam and Dr. Steinman, address the question of how much homology between a self-antigen and a foreign antigen is enough to induce autoimmunity. The researchers in Gautam found that five identical amino acids out of 12 could trigger neuroinflammation, in the form of experimental autoimmune encephalomyelitis (EAE; the animal model of MS). The amino acids only need to be in identical locations and do not have to be in consecutive order. Gautam 3 at 60. According to Dr. Steinman, the three papers collectively demonstrate that a sequence of five out of 12 amino acids is sufficient to lead to neurologic disease. Tr. at 30; Gautam 1; Gautam 2; Gautam 3.

With respect to the BLAST search in this case, Dr. Steinman noted that the sequence "RAGAEPAPRP" from orexin is structurally similar to "RAGTVGEPVP" from the HPV 11 L1 protein in the Gardasil vaccine. First Steinman Rep. at 13-14. Through his BLAST search, Dr. Steinman identified a five amino acid overlap in this region (RAG_ _ _ _P_P). Dr. Steinman opined that the Gautam papers demonstrate that this is sufficient to induce autoimmunity via the mechanism of molecular mimicry.

[9] Dr. Steinman has advanced two different theories in this case. One theory proposes mimicry between the orexin receptor and the Gardasil vaccine. Because I find his theory concerning orexin itself to be more persuasive, I have focused my analysis in that area.

Dr. Fujinami disagreed that the Gautam papers support causation in this case. He opined that the use of complete Freund's adjuvant (CFA) was necessary to induce disease in those studies. Tr. at 90. Unlike CFA, Dr. Fujinami remarked that alum (used in the Gardasil vaccine) is a weak adjuvant. *See* Second Fujinami Rep. at 1. Dr Fujinami opined that alum was not potent enough to cause disease, and further, that it has been shown to have protective effects.

Dr. Fujinami referenced the Sicotte and Wallberg papers. These authors individually studied the effects of immunization on genetically susceptible animals with myelin adsorbed in alum and found that those animals did not develop any autoimmune neuroinflammatory CNS disease, or EAE. First Fujinami Rep. at 2-3; *see also* Sicotte; Wallberg. The papers actually found that mice vaccinated with myelin adsorbed with alum protected the mice from EAE. Wallberg at 1539; Sicotte at 259. Based on these studies, Dr. Fujinami opined that "[t]he Sicotte et al and Wallberg et al articles support my argument (presented in my previous report) that the mimicking epitope in hypocretin/HPV given to an individual in alum would protect from disease (neuroinflammation) rather than induce destruction of the neurons involved in narcolepsy." Second Fujinami Rep. at 1. At the entitlement hearing, Dr. Fujinami testified that "depending on the type of adjuvant you use, you can either protect against autoimmune disease or you can induce autoimmune disease." Tr. at 90.

In response to Dr. Fujinami's position, Dr. Steinman identified the Souayah paper as significant to his theory that the Gardasil vaccine induces an abnormal immune response, and in concert with the amino acid sequences he identified via BLAST search, as to how the HPV vaccine causes narcolepsy. The Souayah paper notes that the Gardasil vaccine results in a 40 fold increase in HPV antibodies when compared with HPV infection. Tr. at 67; Souayah at 888. According to Dr. Steinman, this stronger immune response can lead to autoimmunity. Tr. at 67.

Ultimately, I find Petitioner's position to be more persuasive on this issue. While Dr. Fujinami's cited literature does show that alum was associated with protection from disease in two studies, this finding should not be extrapolated to every covered alum-containing vaccine (DTaP, Tdap, Hep A, Hep B, Hib, pneumococcal, and HPV).[10] This would suggest that every covered vaccine containing alum would protect from autoimmune disease, a conclusion that would seemingly run counter to at least one injury on the Vaccine Injury Table (tetanus toxoid containing vaccines-brachial neuritis).

*ii. Step 2: The Latorre Paper*

While molecular mimicry is a theory that is generally accepted in the Vaccine Program, a "simple invocation of the term generally does not carry a petitioner's burden of proof." *Deshler v. Sec'y of Health & Hum. Servs.*, No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Hum. Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 18, 2019)). This is in part because "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio v. Sec'y of Health & Hum. Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr.

[10] CDC, Vaccine Safety, www.cdc.gov/vaccinesafety/concerns/adjuvants.html (last accessed August 10, 2023).

Dec. 19, 2019), *mot. for rev. denied*, 149 Fed. Cl. 448 (2020); *see also Caredio v. Sec'y of Health & Hum. Servs.*, No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021), *mot. for rev. denied*, 2021 WL 6058835 (2021) ("demonstration of homology alone is not enough to establish a preponderant causation theory") (citing *Schultz v. Sec'y of Health & Hum. Servs.*, No. 16-539V, 2020 WL 1039161, at *22 n. 24 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) ("[m]ere demonstration of theoretical homology alone, based on computer-driven searches involving databases of amino acid sequences, does not carry the day")).

Dr. Steinman opined that the Latorre paper fills this gap. In Latorre, the authors collected blood samples from sixteen patients with type 1 narcolepsy, from three patients with type 2 narcolepsy, and from 13 controls who had the HLA-DQB1*0602 allele but did not have narcolepsy. *Id.* They tested the samples and found orexin-specific CD4+ cells in all 19 patients with type 1 and type 2 narcolepsy. *Id.* Specifically, "the epitope RAGAEPAPRP was identified as being a target of cytotoxic T cells found in the cerebrospinal fluid in patients with Type 1 narcolepsy." Second Steinman Rep. at 5. RAGAEPAPRP is the same amino acid sequence found in orexin that is homologous to the L1 protein in the Gardasil vaccine. Latorre's findings that are pertinent to this case are depicted below:

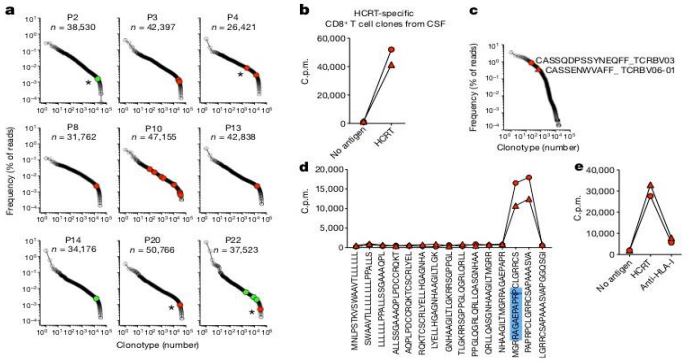


**Fig. 4 | Autoreactive CD4$^+$ and CD8$^+$ T cell clonotypes in blood and CSF of patients with narcolepsy. a**, TCR Vβ CDR3 sequences of autoreactive CD4$^+$ T cell clones can be found in the blood of the same or of different patients with narcolepsy. TCR Vβ sequencing was performed on memory CD4$^+$ T cells ex vivo, after sorting from peripheral blood of patients with narcolepsy. The frequency distribution of all TCR Vβ clonotypes is shown (*n* indicates total number of clonotypes). Coloured circles indicate TCR Vβ clonotypes identical to those found in HCRT-specific (red) and TRIB2-specific (green) CD4$^+$ T cell clones isolated from the same patient. Asterisk indicates TCR Vβ clonotypes found in autoreactive CD4$^+$ T cell clones isolated from a different patient. TCR Vβ sequencing was performed also on samples from patients P1, P5, P7, P9, P11, P12, P16, P17 and P24 and from 13 healthy controls (see Extended Data Fig. 5). In these samples, no sequences of autoreactive T cell clones were found. **b**, Two HCRT-specific CD8$^+$ T cell clones (red circle, clone 1; red triangle, clone 2) were isolated from the CSF of a patient with NT2 with recent disease onset (P14). The proliferation measured after a 16-h pulse with [$^3$H]thymidine is expressed as c.p.m. **c**, Frequency of the identified HCRT-specific CD8$^+$ T cell clones (red circle and triangle) in CSF. TCR Vβ sequencing was performed on CD8$^+$ T cells sorted from in vitro-expanded CSF T cells. **d**, Epitope mapping of the identified HCRT-specific CD8$^+$ T cell clones from the CSF. Epitopes were identified by screening the CD8$^+$ T cell clones against overlapping peptides that span the entire length of HCRT. **e**, MHC restriction of the HCRT-specific CD8$^+$ T cell clones was evaluated by measuring their proliferation against HCRT peptide pool alone or in combination with MHC-class-I blocking antibody.

Latorre at 67.[11]

This second step in Dr. Steinman's theory is an important one. When Dr. Steinman only presents BLAST search sequence homology in a given case, the Respondent's expert typically remarks that this is insufficient to show that the particular homology would cause disease. Indeed in this case, before Petitioner filed the Latorre study, Dr. Fujinami stated: "it has not been proven that there are any pathogenic "disease-relevant" mimicking peptides in the HPV vaccine as opined by Dr. Steinman." First Fujinami Rep. at 3. By citing Latorre, Dr. Steinman has demonstrated that

[11] Although the highlighted region is difficult to read, it is the amino acid sequence "RAGAEPAPRP".

the orexin peptide targeted in type 1 narcolepsy has sequence homology with a component of the Gardasil vaccine.

Dr. Fujinami disagreed with Dr. Steinman on the import of the Latorre paper. He testified it is not clear that the T cells discussed by the authors are pathogenic. Tr. at 103-04. However, the Latorre authors discuss the pathogenic potential of both CD8+ and CD4+ T cells.

> CD8+ T cells have the potential to directly kill HCRT neurons… By contrast, auto reactive CD4+ T cells may have an indirect effect that promotes the generation of pathogenic CD4+ T cells or autoantibodies… By producing high levels of IFNγ and GM-CSF, autoreactive CD4+ T cells may also promote local inflammation and loss of integrity of the blood-brain barrier, triggering the influx of effector inflammatory cells and pathogenic antibodies.

Latorre at 67. Further, in describing one patient with type 2 narcolepsy who had recently developed cataplexy (thus qualifying him for a type 1 narcolepsy diagnosis), the authors noted, "The previous finding of relatively high levels of CD4+ and CD8+ T cells against [orexin] in this patient would be consistent with an autoimmune attack that has not (yet) led to a complete loss of neurons that produce [orexin]." Latorre at 67. Although the authors indicate there is a question about the pathogenic role of CD4+ and CD8+ T cells in narcolepsy, they do find this above-noted evidence to be "consistent" with an autoimmune attack. *Id*. I find the Latorre paper to be persuasive evidence in support of *Althen* prong one.

b. Epidemiology

Respondent cited to the Torstensen study, a sample of 29 girls and women in Denmark who were evaluated for their sleep complaints after receiving the HPV vaccine. Torstensen. Torstensen stated "[w]e here aimed to evaluate whether sleep-related symptoms following HPV vaccination could be associated with development of narcolepsy type 1." *Id*. at 1. Testing was conducted to confirm whether these sleep complaints were diagnostic of type 1 narcolepsy; testing included polysomnographs, MLST, genetic testing for HLA-DQB1*06:02, and CSF for hypocretin-1. *Id*. at 2. The authors noted that "[t]he study was not designed to assess with epidemiological tools the prevalence of type 1 narcolepsy in the vaccine group compared with the background population." *Id*. at 3. The authors concluded that none of the subjects met the requirements for a type 1 narcolepsy diagnosis. *Id*. The authors further concluded that there was no association between the HPV vaccine and the development of type 1 narcolepsy; a conclusion that appears to be based on the fact that none of the 29 subjects had narcolepsy. *Id*. ("If there was any association with narcolepsy type 1, one would expect to identify this association in this particular group of individuals."). Because of this unique set of circumstances, I do not find the Torstensen paper to be especially persuasive in this case as it pertains to the question of vaccine causation. The stated aim of the study was to evaluate whether the symptoms reported by the study participants were associated with narcolepsy, not to assess "the prevalence of type 1 narcolepsy in the vaccine group compared with the background population." *Id*. at 3.

Respondent also cited to Arnheim-Dahlstrom for epidemiological support. Arnheim-Dahlstrom was a wide cohort study of adverse events after HPV vaccination in adolescent girls in

Denmark and Sweden between 2006-2010. Arnheim-Dahlstrom at 1. The authors conclude that there is "no evidence supporting associations between exposure to [HPV] vaccine and autoimmune, neurological, and venous thromboembolic adverse events." *Id.* The Arnheim-Dahlstrom study supports Respondent's position that the HPV vaccine did not cause Petitioner's narcolepsy.[12]

Dr. Fujinami filed two WHO reports regarding narcolepsy and the H1N1 Pandemrix vaccine. Ex. C, Tabs 8, 9. In the 2013 WHO Report, it was noted that there was a possible increased risk for adults to develop narcolepsy after the H1N1 vaccination but risk was lower in children. Ex. C, Tab 8 at 12. The same report did not mention any connection between the HPV vaccine and narcolepsy. The 2015 WHO Report stated that increased risk had been consistently produced in H1N1 vaccine/narcolepsy study results. Ex. C, Tab 9 at 8. The report also discussed the general safety of the HPV vaccine but not in conjunction with narcolepsy. *Id.* at 6-8.

The experts agree that the Pandemrix vaccine has been linked to an increased risk of developing narcolepsy. The experts also agree that "molecular mimicry has been hypothesized to be the cause of the regional epidemic of narcolepsy caused by the Pandemrix flu vaccine in 2009 and 2010." Brown Rep. at 6; Tr. at 37 (Dr. Steinman); Tr. at 154 (Dr. Fujinami).

When presented, epidemiological may be relevant evidence that bears on the causation analysis. *D'Toile,* 2016 WL 7664475 at *22; *see also W.C.*, 704 F.3d at 1361 (special master was not arbitrary in denying compensation, and noting that the special master properly relied on several epidemiological studies in reaching his decision); *Lampe*, 219 F.3d at 1365 (stating "[a]n epidemiological study may be probative medical evidence relevant to a causation determination"); *C.K. v. Sec'y of Health & Hum. Servs.*, 113 Fed. Cl. 757, 770 (2013) (a special master may evaluate contradictory evidence offered by Respondent). At the same time, petitioners need not offer epidemiologic evidence to meet their burden under *Althen*. *See Andreu,* 569 F.3d at 1378-79 (citing *Capizzano*, 440 F.3d at 1325-26). Indeed, because vaccine injuries are rare events, the fact that a particular epidemiologic study suggests a vaccine is generally safe should not prevent a claimant from prevailing. *See Harris v. Sec'y of Health & Hum. Servs.*, No. 10–322V, 2014 WL 3159377, at *11 (Fed. Cl. Spec. Mstr. June 10, 2014) (epidemiologic studies cannot absolutely refute causal connections, because it is possible that a larger study could always detect an increased risk). Although I have considered the epidemiologic evidence filed in this case, I do not find that it prevents Petitioner from meeting his burden.

c. Other Vaccine Program Cases

[12] According to Dr. Steinman, the Arnheim-Dahlstrom paper demonstrated an increased rate of narcolepsy after HPV vaccination, even though it "did not reach 'statistical significance'." First Steinman Rep. at 26. He argued that the paper shows the incidence rate for the vaccinated (2.61) is higher than the unvaccinated (1.81). However, this position is not consistent with the authors' conclusion, that there is no increase of autoimmune, neurological, or venous thromboembolic adverse events after the HPV vaccine. Arnheim-Dahlstrom at 8. Ultimately, I am not persuaded by Dr. Steinman's position on this issue.

A number of cases alleging narcolepsy have been filed in the Vaccine Program. Although prior decisions from different cases do not control the outcome herein (*Boatmon*, 941 F.3d at 1358-59), I will discuss several cases with similar theories of causation.

One special master found that Dr. Steinman presented a persuasive theory as to how the FluMist vaccine could cause type 1 narcolepsy, though she denied entitlement based on *Althen* prongs two and three. *Henkel v. Sec'y of Health & Hum. Servs.*, No. 15-1048V, 2022 WL 16557979 (Fed. Cl. Spec. Mstr. Aug. 31, 2022); *mot. for rev. denied*, 165 Fed. Cl. 153; *appeal docketed*, No. 23-1894 (Fed. Cir. May 17, 2023). The *Althen* prong one theory presented by Dr. Steinman in *Henkel* was virtually identical to the one advanced in the case at bar.

The other special masters who have recently evaluated this question have determined that petitioners did not advance persuasive causal theories. Although *A.T.* involved a claim similar to that of Mr. Cobb, the Respondent in *A.T.* presented studies that were not discussed in this case and generally defended the case differently.[13] *A.T. v. Sec'y of Health & Hum. Servs.*, No. 16-393V, 2021 WL 6495241 (Fed. Cl. Spec. Mstr. Dec. 17, 2021). Respondent also refuted Dr. Steinman's molecular mimicry theory through discussion of the Silvanovich paper, an analysis that was not conducted here. In *E.S.*, Petitioner was diagnosed with narcolepsy type II, which is arguably not an auto-immune condition; and further, was not diagnosed until years after vaccination. *E.S. v. Sec'y of Health & Hum. Servs.*, No. 17-480V, 2020 WL 9076620 (Fed. Cl. Spec. Mstr. Nov. 13, 2020).

The remainder of the narcolepsy cases were decided before the Latorre paper was published. *Dougherty v. Sec'y of Health & Hum. Servs.*, No. 15-1333V, 2018 WL 3989519 (Fed. Cl. July 5, 2018), *mot. for review den'd,* 141 Fed. Cl. 223 (2018) (flu vaccine and narcolepsy); *McCollum v. Sec'y of Health & Hum. Servs.*, No. 14-790V, 2017 WL 5386613 (Fed. Cl. Sept. 15, 2017); *mot. for review den'd,* 135 Fed. Cl. 735 (2017), *aff'd,* 760 F. App'x 1003 (Fed. Cir. 2019) (flu vaccine and narcolepsy); *D'Toile v. Sec'y of Health & Human Servs.*, No. 15-085V, 2016 WL 7664475 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *mot. for review den'd,* 2017 WL 2729570 (Fed. Cl. Mar. 2, 2017), *aff'd,* 726 F. App'x 809 (Fed. Cir. 2018) (FluMist vaccine and narcolepsy); *Garrison v. Sec'y of Health & Hum. Servs.*, No. 14-762V, 2015 WL 7424016 (Fed. Cl. Spec. Mstr. Oct. 29, 2015) (finding Petitioner met her burden in a flu vaccine narcolepsy case where Respondent did not present his own expert opinion).

[13] For example, Respondent's expert cited Hvid et al., *Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases*, 283 JOURNAL OF INTERNAL MEDICINE 154-65 (2018) as additional epidemiological evidence in support of their position. Hvid was a population based study of all women aged 18-44 in Denmark and Sweden who received the quadrivalent HPV vaccine between 2006-2010. Although a number of narcolepsy cases post-vaccination were reported, the authors of the Hvid paper found there was no association between narcolepsy and the HPV vaccine. Respondent also cited Phillips et al., *Safety of Human Papillomavirus Vaccines: an Updated Review*, 41 DRUG SAF. 329 (2018). This review "identified 109 studies, including 15 population-based studies in over 2.5 million vaccinated individuals across six counties. All vaccines demonstrated an acceptable safety profile." I further note that in this case, Respondent elected not to conduct a cross examination of Dr. Steinman, although Respondent's current counsel of record was not present at the entitlement hearing.

"[T]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. "[C]lose calls regarding causation are resolved in favor of injured claimants." *Id*. This case is indeed a close call. Ultimately, I find that Petitioner has presented preponderant evidence in support of his causal theory that molecular mimicry between components of orexin and a portion of the Gardasil vaccine "can cause" type 1 narcolepsy.

2. *Althen* Prong Three

The timing prong contains two parts. First, Petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and second, they must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.,* 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013).

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Hum. Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Grant*, 956 F.2d at 1148 ("[T]he inoculation is not the cause of every event that occurs within the ten[-]day period ... [w]ithout more, this proximate temporal relationship will not support a finding of causation." (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

Petitioner developed the onset of narcolepsy between one and three weeks after his third HPV vaccination. Petitioner's medical records consistently reflect this window of onset. *See* Ex. 2 at 13 (medical record from November 17, 2015 where Petitioner told Dr. Miller he had really low energy since school started and feels tired all the time); Tr. at 6-7 (Petitioner's testimony that school started at the end of August); Ex. 6 at 33 (medical record from November 23, 2015 where Petitioner reported three months of fatigue to Dr. Strehle); Ex. 3 at 5 (medical record from December 29, 2015 where Petitioner's history of presentation was noted to have begun in late August); Ex. 1 at 1-3 (April 4, 2016 visit with Dr. Gutu where the medical record documents that Petitioner had a mono-like illness in late August-September which resulted in excessive fatigue).

Dr. Steinman conceded that there are no studies regarding the appropriate onset interval for narcolepsy after HPV vaccine that are directly applicable to this case. Tr. at 69. He opined that the Schonberger and Langmuir studies are analogous to this case and support the onset of narcolepsy approximately two weeks after vaccination. Tr. at 70-71. Schonberger et al., *Guillain Barre Syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977*, 110 AMERICAN JOURNAL OF EPIDEMIOLOGY 2, 105-23, (1979) (filed as Ex. 50) (hereinafter "Schonberger"). Schonberger demonstrates that the swine flu vaccine can cause Guillain Barré syndrome (GBS), a demyelinating disease of the peripheral nervous system. The increased risk for developing GBS after swine flu vaccination was concentrated within the five weeks after vaccination but extended up to eight weeks after vaccination. Schonberger at 105. Langmuir found an increased risk of developing GBS within six weeks of receipt of the H1N1 vaccination. Langmuir et al., *An Epidemiologic and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines*, 119 AM

J EPIDEMIOL 841-79 (1984) (filed as Ex. 49).

Dr. Steinman also cited to Souayah et al., who reviewed VAERS data from 2006-2009 identifying cases of GBS after the Gardasil vaccine. Souayah at 886. At the entitlement hearing, Dr. Steinman testified that the "onset of symptoms was within six weeks after [Gardasil] vaccination in 70 percent of the patients in whom the date of vaccination was known." Tr. at 71. Dr. Steinman also testified that this article provided additional support for the temporal interval between Petitioner's third Gardasil vaccination and the onset of his type 1 narcolepsy. *Id*. at 70 (Dr. Steinman testifying that this window is "typical of an autoimmune reaction causing a neuroinflammatory condition").

I find that between one and three weeks is a medically acceptable timeframe to infer causation. Although Schonberger and Langmuir involve the onset of GBS after swine flu vaccine, I find Dr. Steinman provided persuasive testimony on the applicability of those studies to the present case. Additionally, the Souayah article, which pertains to the HPV vaccine and GBS also provides support for the temporal interval in the case at bar. Although none of the three studies involves Petitioner's same vaccine and condition, they all support the point that an adaptive immune reaction would likely cause the onset of a neuroinflammatory condition within several weeks of vaccination. Petitioner has satisfied the third *Althen* prong.

3. *Althen* Prong Two

Under *Althen's* second prong, Petitioner must "prove a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." *Id*. Petitioner is not required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Id*. (omitting internal citations). *Capizzano v. Sec'y of Health & Hum. Servs*., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second *Althen* prong. *Isaac v. Sec'y of Health & Hum. Servs.*, No. 08-601V, 2012 WL 3609993, at *25 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev.* denied, 108 Fed. Cl. 743 (Fed. Cl. 2013), *aff'd*, 540 Fed.Appx. 999 (Fed. Cir. 2013).

In this case, the evidence of Petitioner's medical history is undisputed. Petitioner was healthy prior to vaccination. Between one to three weeks after receipt of the third dose of the HPV vaccine, he developed excessive fatigue, which constituted the onset of his type 1 narcolepsy. Although the cause of type 1 narcolepsy is unknown, researchers believe that the loss of orexin-producing neurons may be initiated by "immunological responses that manifest in genetically predisposed individuals upon triggering by environmental factors." Latorre at 63. Petitioner's medical course is consistent with his theory of molecular mimicry.

When a petitioner has established that vaccination can cause a given condition and has demonstrated that the timing prong has also been met, it allows the petitioner to establish that vaccination was a but-for cause of his condition. The Federal Circuit has provided guidance with respect to this issue. "Evidence demonstrating petitioner's injury occurred within a medically

acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the "but-for" prong of the causation analysis." *Capizzano*, 440 F.3d at 1326 (finding medical opinions that explain how a vaccine can cause the injury alleged coupled with evidence demonstrating a close temporal relationship "are quite probative" in proving actual causation). *Pafford*, 451 F.3d at 1358*; see also Contreras*, 107 Fed. Cl. at 295, (finding that there is a "logical overlap between the three *Althen* prongs, and that evidence that goes to one prong may also be probative for another prong"). Petitioner has met the second *Althen* prong.

## VII. Conclusion

Upon careful evaluation of all the evidence submitted in this matter, including the medical records, the affidavits and testimony, as well as the experts' opinions and medical literature, I conclude that Petitioner has preponderantly demonstrated that he is entitled to compensation under the Vaccine Act. An order regarding damages will issue shortly.

**IT IS SO ORDERED.**

**s/ Katherine E. Oler**
Katherine E. Oler
Special Master