In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 17-181V

Filed: September 27, 2024

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NICOLE GIRARDI, *

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Petitioner, *

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v. *

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SECRETARY OF HEALTH *
AND HUMAN SERVICES, *

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Respondent. *

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Mark Sadaka, Esq., Law Offices of Sadaka Associates, LLC, Englewood, NJ for petitioner.
Zoe Wade, Esq., U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On February 7, 2017, Nicole Girardi ("Ms. Girardi" or "petitioner") filed a petition under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 *et seq.*[2] ("Vaccine Act" or "the Program"). Petitioner alleges that the third dose of Cervarix, a human papillomavirus ("HPV") vaccine, that she received on March 20, 2014 caused her to develop optic neuritis and related symptoms. She also alleges that, in the alternative, the vaccination she received on March 20, 2014 significantly aggravated her optic neuritis and related symptoms. *See* Petition ("Pet.") at 1, ECF No. 10.

Having reviewed the record, expert reports, associated literature, and heard testimony at hearing, I find that petitioner has preponderantly established that the Cervarix vaccine triggered her optic neuritis and did so in a medically relevant timeframe.

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[1] Because this Ruling contains a reasoned explanation for the action taken 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, the undersigned finds that the identified material fits within this definition, such material will be redacted from public access.

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

I. Overview of the Claim and Injury

Petitioner claims that she suffered optic neuritis 38 days after receiving her third dose of Cervarix, a bivalent HPV vaccine which protects against HPV types 16 and 18.

A. Human Papillomavirus Infection and Cervarix

Human papillomavirus infection is the most common sexually transmitted infection in the United States. Most HPV infections cause no symptoms and the body's immune system clears 90% of the virus naturally within two years. Persistent genital HPV infections can cause cancer in women and other types of anogenital cancers or genital warts in both men and women. Pet. Ex. 24[3] at 2. HPV is transmitted through direct contact with the lesions or warts that develop as a result of HPV infection, generally through sexual contact. Up to 70% of sexually active women will be infected with at least one HPV within the first five years of initial sexual encounter. Pet. Ex. 23[4] at 534.

Three HPV vaccines have been licensed for use in the United States: the nine-valent Gardasil 9 and the quadrivalent Gardasil 4, both manufactured by Merck, and Cervarix, a bivalent vaccine manufactured by GlaxoSmithKline. Pet. Ex. 24[5] at 2.

The Cervarix vaccine is an AS04-adjuvanted vaccine that contains recombinant L1 protein, of oncogenic HPV types 16 and 18. The adjuvant AS04 is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on to aluminum (as hydroxide salt). Pet. Ex. 32[6] at 1, 12. The most common adverse reactions contained in the package insert are pain, redness, and swelling at the injection site, and fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgias. *Id.* at 1, 3.

B. Optic Neuritis

Optic neuritis is an inflammation of the optic nerve that can be caused by infection and immune-related illnesses. Pet. Ex. 22 at 1. Optic neuritis is associated with evidence of white matter lesions in a large proportion of patients, suggesting that optic neuritis may be considered an early or subclinical form of multiple sclerosis[7] ("MS"). Pet. Ex. 30[8] at 1. Literature suggests that patients with optic neuritis have more anti-myelin basic protein antibodies and anti-proteolipid protein antibodies than control subjects, though there was no difference between idiopathic optic neuritis and optic neuritis as a symptom of MS. *Id.*

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[3] Gayathri Sridhar et al., *Evaluation of optic neuritis following human papillomavirus vaccination*, 13 HUMAN VACCINES & IMMUNOTHERAPEUTICS 1705 (2017), filed as "Pet. Ex. 24."

[4] INST. OF MED., ADVERSE EFFECTS OF VACCINES: EVIDENCE & CAUSALITY (Kathleen Stratton et al. eds., 2012), filed as "Pet. Ex. 23."

[5] Sridhar et al., *supra* note 3.

[6] *Cervarix Highlights of Prescribing Information*, GlaxoSmithKline, filed as "Pet. Ex. 32."

[7] MS is an autoimmune disease characterized by demyelinated plaques in the central nervous system infiltrated by T cells, B cells, and macrophages. Pet. Ex. 30 at 1.

[8] F. Sellebjerg et al., *Acute Optic Neuritis: Myelin Basic Protein and Proteolipid Protein Antibodies, Affinity, and the HLA System*, 38 ANNALS OF NEUROLOGY 943 (1995), filed as "Pet. Ex. 30" and "Pet. Ex. 46."

While optic neuritis has been reported following HPV vaccines in large scale studies, these studies have concluded that there was no evidence that vaccines are associated with development of optic neuritis in the four-to-six-week period following immunization. The studies purportedly had sufficient power to detect small excess risk. Pet. Ex. 42[9] at 2-3.

II. Procedural History

The petition was filed on February 7, 2017 and the matter was assigned to the undersigned. ECF No. 1, 4. Petitioner then filed an amended petition on February 10, 2017. ECF Nos. 7-10.

Following a status conference on April 20, 2017, petitioner filed medical records on April 25 and 26, 2017; June 20, 2017; and July 25, 2017.[10] Petitioner's Exhibit ("Pet. Ex.") 1-11, ECF Nos. 16-17; Pet. Ex. 12, ECF No. 18; Pet. Ex. 13, ECF No. 20.

Respondent filed his Rule 4(c) Report on October 20, 2017, recommending against compensation. ECF No. 25.

Petitioner filed an expert report from Dr. Lawrence Steinman on March 21, 2018, along with his curriculum vitae and the medical literature cited in the report. Pet. Ex. 15-40, ECF No. 28. Respondent filed expert reports from Dr. Tim Lotze and Dr. J. Lindsay Whitton on September 19, 2018, along with each expert's curriculum vitae and corresponding medical literature. Respondent's Exhibit ("Resp. Ex.") A-D, ECF Nos. 31-32.

Following a status conference held on December 7, 2018, petitioner filed additional medical records and a supplemental report and medical literature from Dr. Steinman on July 3, 2019. Pet. Ex. 9, 14, ECF No. 37; Pet. Ex. 41-47, ECF No. 41-42. Thereafter, respondent filed supplemental expert reports and medical literature from Drs. Lotze and Whitton on October 7, 2019. Resp. Ex. E, ECF No. 44; Resp. Ex. F, ECF No. 45.

A Rule 5 conference was held on December 16, 2019, after which petitioner was directed to submit a demand to respondent. The parties were also to discuss dates for an entitlement hearing. ECF No. 46.

Petitioner confirmed that she submitted a demand to respondent, but respondent advised that he intended to continue defending the case. An entitlement hearing was scheduled for March 7 and 8, 2022. ECF Nos. 48-49, 51.

Petitioner filed her pre-hearing submission on January 18, 2022, and additional medical literature on January 28, 2022. ECF No. 62, 64. Respondent filed his responsive pre-hearing submission on February 7, 2022, and petitioner replied on February 22, 2022. ECF Nos. 65, 66. The parties filed a joint pre-hearing submission on February 28, 2022. ECF No. 69.

[9] Roger Baxter et al., *Case-centered Analysis of Optic Neuritis After Vaccines*, 63 CLINICAL INFECTIOUS DISEASES 79 (2016), filed as "Pet. Ex. 42" and "Resp. Ex. A, Tab 7."
[10] Documents were routinely filed, stricken, and refiled by counsel.

An entitlement hearing was held on March 7, 2022, and additional evidence was ordered to be filed following the hearing. ECF No. 71. Petitioner filed additional evidence on April 6, 2022, and updated medical records on May 6, 2022. ECF Nos. 74, 76. The parties filed simultaneous post-hearing briefs on October 4, 2022. ECF Nos. 81-83.

The matter is now ripe for an entitlement decision.

III. The Factual Record

A. Petitioner's Medical History Prior to the Third HPV Vaccination

Petitioner was born on March 11, 1999. She enjoyed a normal healthy childhood, suffered from the usual childhood illnesses, and had no history attributable to the injuries alleged in this case. She received all vaccines without event. *See generally* Pet. Ex. 1; Pet. Ex. 13 at 1. She wore glasses with vision corrected to 20/20 since 7th grade. *See generally* Pet. Ex. 4.

Petitioner received her first two Cervarix vaccinations on June 25, 2013 and August 27, 2013. Pet. Ex. 13 at 1. There were no reactions documented following these vaccinations.

She received the subject third Cervarix vaccination on March 20, 2014. Pet. Ex. 13 at 1.

B. Petitioner's Medical History Following the Third HPV Vaccination

Petitioner presented to the pediatrician on May 5, 2014, with a one-week history of headache. Pet. Ex. 1 at 69. She was diagnosed with tension headaches following a normal examination and was to follow up in a week. Pet. Ex. 1 at 71.

Petitioner returned to the pediatrician the following day reporting daily frontal headaches for the past seven to nine days that come and go but are always there somewhat. Pet. Ex. 1 at 72. She complained of pressure and pain behind her eye and pressure above her eye in her forehead. She had nasal congestion and was taking Advil three times a day along with an over-the-counter allergy pill. She had no history of headaches or sinus infections. *Id*. The examination was normal, and the assessment was acute sinusitis. She was prescribed amoxicillin and Flonase nasal spray. Her doctor suggested seeing a neurologist for the headaches. *Id*. at 74.

On May 7, 2014, petitioner presented to Somerset Medical Center Emergency Room ("ER") with ten days of right-sided headache, increasing since Saturday. She had been prescribed an antibiotic for sinusitis without relief. Pet. Ex. 8 at 8, 13. A head CT revealed prominent adenoidal tissue with posterior nasopharynx but was otherwise normal. *Id*. at 19-20. She was treated with Toradol, Reglan, Benadryl, and IV fluids. *Id*. at 66, 69. She noted improvement but still had pain when she moved her eye. *Id.* at 69. The discharge diagnosis was headache. *Id*. at 70.

Petitioner presented to a neurologist on May 9, 2014, reporting severe headache since April 28, 2014, with minimal relief from Advil. Pet. Ex. 3 at 8. She began to suffer from pain behind her right eye and forehead on Saturday. She saw the pediatrician twice and was diagnosed with sinusitis and treated with amoxicillin, but she continued to have a headache with right eye pain

and some blurry vision. She presented to the ER on May 7, 2014, and had a normal CT scan of the head. She received IV hydration, Reglan, Benadryl, and Toradol, which relieved the headache, but it returned after discharge. *Id*. Petitioner was noted to be a straight A student in advanced classes with no history of concussion or seizures. *Id*. Her mother had a history of migraines, and her brother had headaches. *Id*. at 9. The assessment was migraines. *Id*. at 10.

On May 21, 2014, petitioner presented to her ophthalmologist Dr. Wasserman for an emergency visit for right eye pain. She complained of blurred vision for one week and significant headache for over a month. Pet. Ex. 5 at 2.[11] Examination revealed "light perception only" with an "afferent pupillary defect" and she could not read any color plates with her right eye. A dilated retina exam revealed a diffusely edematous and hemorrhagic right optic nerve with associated retinal hemorrhages and exudates on the right side. The left eye was unremarkable. *Id*. Dr. Wasserman suspected optic neuritis and arranged for an emergent referral to Wills Eye Hospital ("Wills Eye") in Philadelphia. *Id*. at 1-2.

Petitioner presented to Wills Eye that day. She reported 33 days of headaches and three weeks of right-sided head pain with mildly blurred vision worseing over the past week. She was "[r]ecently immunized for HPV in April." There was no viral prodrome or other neurological symptoms and no tick or cat exposure. Pet. Ex. 6 at 27-28; Pet. Ex. 7 at 29. A brain MRI showed diffuse enlargement and enhancement of the entire right optic nerve with extension to the optic chiasm on the right, consistent with optic neuritis. She had no brain lesions and no intracranial mass. Pet. Ex. 7 at 156-59. She was admitted and treated with "pulse steroids" for right optic neuritis of unclear etiology. *Id.* at 38. CSF testing showed elevated glucose but was otherwise normal. Her antineutrophil cytoplasmic antibody tests were all negative, as was ANA. *Id*. at 58. Her vision was significantly improved after three days of pulsed steroids, and she was discharged with a course of oral steroids. She was to follow up with ophthalmology and the Multiple Sclerosis Clinic ("MS Clinic") at Thomas Jefferson University in one week. She had no activity restrictions. *Id*.

Petitioner presented for follow-up at the MS Clinic on May 30, 2014. Her vision continued to improve, her blood work was normal, and she had no lesions on the brain. Pet. Ex. 6 at 6. A follow-up vision check was planned for two weeks later, after the prednisone taper. *Id*. at 8.

Petitioner returned for follow-up on June 13, 2014. Pet. Ex. 6 at 4. She was no longer taking any medications and had significant improvement in vision and color. Humphrey vision field ("HVF") testing showed "supratemp/paracentral defect." *Id*. She was doing well, was to follow up with the neurologist the following week, and return for a vision check in two to three months. HVF testing was planned to be repeated in six months. *Id*.

Petitioner followed up with Dr. Leist, a neurologist, on June 18, 2014. Pet. Ex. 3 at 4. Dr. Leist documented a 15-year-old female recently diagnosed with right optic neuritis. She had onset of severe headaches accompanied by right eye pain in April 2014, was diagnosed with sinusitis and treated with antibiotics, and was then diagnosed with migraines. Her ophthalmologist suspected optic neuritis, and she was taken to Wills Eye. *Id*. at 4. An MRI of the brain was normal, but MRI of the orbits of the eye showed demyelinating white matter lesions diagnosed as optic

[11] Dr. Wasserman's records can also be found in Pet. Ex. 9.

neuritis. *Id*. at 4, 22-25. Her right eye pain and headaches completely resolved after three days of IV steroids, but her vision was still blurry. *Id*. at 4. Dr. Leist explained that the risk of developing MS based on her diagnosis of optic neuritis was one in five, but assured her and her family that she had a normal brain MRI, which was favorable. He advised that her vision may not return completely to baseline after an episode of optic neuritis. *Id*. at 5. Her CSF was normal except for elevated glucose. Serum ANA, NMO antibody, and Lyme testing were also negative. Pet. Ex. 3 at 12-17. She was to be monitored conservatively and follow up with her primary physician or neurologist for management of migraines. *Id.* at 5. Repeat MRI and NMO antibody test would be considered in the future. *Id*. The intake form for the visit completed by petitioner's mother noted Cervarix vaccine as a possible root cause for her optic neuritis. *Id*. at 42.

Petitioner returned to Dr. Leist on August 12, 2014. She had no neurological symptoms, and her vision was almost back to normal. Pet. Ex. 3 at 1. There were no active lesions on the MRI of her brain and cervical spine performed on August 1, 2014. *Id*. at 18-22; Pet. Ex. 7 at 1-4. Dr. Leist's plan was to continue monitoring her condition with a repeat MRI in ten months. Petitioner was to continue her normal daily activities. Pet. Ex. 3 at 1.

Petitioner returned to Dr. Wasserman on August 26, 2014. She reported no vision problems, was not taking any medication, and was wearing contacts again. Pet. Ex. 5 at 2. On examination, her visual acuity was 20/20, extraocular motility was full, there was no afferent pupillary defect, and color vision was normal. A dilated retinal examination revealed sharp optic nerves bilaterally. Dr. Wasserman wrote, "[t]here may be some residual optic nerve pallor in the right optic nerve." *Id.* at 2-3. There was some old retinal exudate and/or possible subretinal fibrosis that did not appear to be affecting her vision. Visual field testing in the left was normal, and the right looked good with minimal depression of overall vision and a small and large blind spot. *Id*. at 3. Dr. Wasserman concluded that petitioner had an "excellent return of vision" after an episode of optic neuritis. *Id*.

At her return visit to Dr. Wasserman a year later, on August 17, 2015, there were no signs of MS on clinical examination or repeat imaging. She was noted to be doing well. Pet. Ex. 9 at 1. Her eye examination was normal. She had some mild pigmentary changes on the right consistent with old resolved papilledema, but no active disease. The visual field showed a slightly enlarged blind spot on the right eye but was otherwise normal. The impression was resolved optic neuritis on the right side with good visual acuity and color vision. *Id*.

On September 9, 2015, petitioner presented to the pediatrician for a well visit. She was followed at Jefferson for optic neuritis and had "regained most vision". Pet. Ex. 13 at 2. Her vision was 20/20 on the right and 20/16 on the left with contacts. *Id*. at 3. She received a Menveo vaccination without event. *Id*. at 1, 5.

At a visit to the gynecologist in August 2015, bloodwork showed that petitioner had elevated TSH, and she was referred to an endocrinologist for further evaluation. Pet. Ex. 11 at 6; *see* Pet. Ex. 12[12] at 1. She was seen by Dr. Cheruvu in March 2016 and diagnosed with an enlarged

[12] Dr. Cheruvu's records were also filed as Petitioner's Exhibit 10.

thyroid. She was clinically euthyroid[13] but her TSH levels were borderline. Dr. Cheruvu explained that the most common cause of acquired hypothyroidism in the United States is autoimmune thyroid disease. Pet Ex. 12 at 2.

Petitioner filed updated medical records following the hearing. Pet. Ex. 50; Pet. Ex. 51. At petitioner's most recent eye examination in June 2022, Dr. Wasserman noted a history of optic neuritis but no late sequela. Pet. Ex. 52 at 1. He wrote that petitioner subjectively feels her visual acuity was "not as clear" and he noted an objectively small possible visual field defect. Petitioner was to follow up in two to three months. Pet. Ex. 52 at 1.

No further records were filed.

C. Petitioner's Testimony

Petitioner did not submit an affidavit, but she testified at hearing.

At the time of the hearing, petitioner was a recent college graduate with a degree in civil engineering. Tr. 6. She was employed as a civil engineer, designing infrastructure related to electric vehicle charging stations. She was working remotely, with the majority of her work done on a computer. Tr. 6.

Petitioner described optic neuritis as a swelling of the optic nerve which causes vision loss in the affected eye. It is a common symptom in those with MS or Lyme disease. Tr. 7.

According to petitioner, she has underlying damage to her peripheral vision as a result of her optic neuritis, and she suffers from eye strain issues by the end of an eight plus hour workday spent on a computer. Tr. 7-8.

She recalled that she was 15 and in ninth grade when she received her third Cervarix vaccine on March 20, 2014. She was in good health and had 20/20 vision when wearing contacts. Tr. 9. On April 28, 2014, she began to have headaches and recalled texting her mom from dance to tell her she had a really bad headache. Tr. 10. She described pain across the front of her head and especially behind her right eye when she moved her eyes or bent down to pick something up. Tr. 10. She stated that headaches normally are not alarming but hers became increasingly worse as the days went on. Tr. 11. She saw her pediatrician the first week of May but there were no solid answers. The pediatrician thought it was likely dehydration and allergies and suggested petitioner change her clothing after school to ensure allergens did not stick to her clothing. Tr. 11.

Petitioner stated that two days later, she went to school but could not get past first period before calling her mom from the nurse's office. They went to the ER but also did not get solid answers for her pain. Her CT scan was normal. Tr. 11. They gave her pain medicine and "sent me on my way." Tr. 11-12.

[13] Euthyroid refers to "the condition of having normal thyroid function, as opposed to hyperthyroidism and hypothyroidism." *Euthyroidism*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 647 (33rd ed. 2019) [hereinafter "DORLAND'S"].

Petitioner stated that the pain continued, and she went to a neurologist. Based on the normal CT and her examination, the neurologist said it was stress migraines but did not explain the pain behind her right eye. She was prescribed Naproxen and caffeine. Tr. 12. She took the Naproxen but did use caffeine. Tr. 12. The Naproxen gave her moments of relief, but she still had constant pain. Tr. 15.

Petitioner stated, "from the very beginning of the headaches…the pain was based behind my eye." Tr. 12. She recalled learning that there was something going on with her eye around the time she saw Dr. Wasserman on May 21. She started to notice that her eye was blurry, something was "off" with her vision, and things were not clear when she looked around.[14] Tr. 12-13.

Petitioner recalled a conversation with her parents the night before she saw Dr. Wasserman. She told them she still had the headache, and her vision wasn't clear. Her dad told her to cover her left eye and tell him what she saw, and when she did, she only saw gray. Tr. 13-14. They saw Dr. Wasserman emergently the next day. Dr. Wasserman diagnosed her with optic neuritis and explained that the swelling of the optic nerve was making the brain unable to communicate with the eye, so she could not see. Tr. 14. He arranged for petitioner to be seen in Philadelphia that night. Tr. 14.

Petitioner stated they went to Will's Eye in Philadelphia that night and she had a full work up with an MRI. She was admitted for three days of steroid treatment. Tr. 14. Within the first 24 hours of treatment, the pain began to subside and her vision slowly came back. Tr. 15.

Petitioner talked about how the weeks between the onset of the headaches and her hospitalization affected her life and her family and friends. Tr. 16-17. She explained that her peripheral vision is mainly affected now. It is difficult for her to drive at night, and watching TV or movies with subtitles or when she's too close to the screen causes issues with the picture being out of focus. Tr. 18. She has no restrictions on her driver's license other than wearing corrective lenses. Tr. 23. She has never fully recovered due to permanent scar tissue, but the improvement after treatment has remained since then. Tr. 18.

Petitioner described the entire experience as traumatic and painful. She endured two spinal taps and other testing while her doctors were trying to determine what was going on. The numbing agent did not work for one of the spinal taps, and she felt intense pain and burning in her spine. She described feeling frustrated and hopeless. Tr. 19. Petitioner recounted a neurologist she followed up with after her stay at Will's Eye, who told her "the door of normalcy has closed for you as far as . . . my vision and specifically regarding multiple sclerosis, because . . . optic neuritis is something that's commonly seen in patients who develop MS. He told me that I now have about a one in five chance that someday I might develop MS." That possibility has taken an emotional toll. Tr. 20. Beyond the physical pain of the experience, the emotional element sticks with her. Petitioner agreed that she has 20/20 vision with contacts. Tr. 21-22.

[14] Petitioner was reading from notes for the dates and was asked to put her notes away.

D. Petitioner's Notes

Following the hearing, petitioner filed a two-page document titled "Timeline of Symptoms, Actions, and Treatments", which includes the onset of her headache on April 28 and details the course of her medical visits, treatment, and pain. Pet. Ex. 50. Petitioner's timeline is consistent with the medical record.

IV. The Experts

The parties stipulated to the qualifications of the experts prior to the hearing, and each expert was recognized as an expert in his respective field. The three experts in this case are Dr. Steinman, a neuroimmunologist, Dr. Lotze, a neurologist, and Dr. Whitton, a Ph.D. in immunology.

A. Petitioner's Expert, Dr. Lawrence Steinman

1. Dr. Steinman's Reports

Dr. Steinman issued two reports. Pet. Ex. 15; Pet. Ex. 41. Dr. Steinman noted that petitioner had no underlying condition that may have triggered optic neuritis, no infection or local inflammation associated with orbital inflammation, and no history of autoimmune disease. Pet. Ex. 15 at 7. He acknowledged that the most common adverse events associated with the Cervarix vaccine are headaches, fatigue, myalgia, gastrointestinal symptoms, and arthralgia. *Id*.

Dr. Steinman's theory is based on molecular mimicry between the peptide sequences in the Cervarix vaccine and myelin oligodendroglial glycoprotein (MOG), proteolipid protein (PLP), and myelin basic protein (MBP), the myelin antigens that are known autoimmune targets in optic neuritis. Pet. Ex. 15 at 8-9; Pet. Ex. 26[15]; Pet. Ex. 27[16]; Pet. Ex. 28[17]; Pet. Ex. 29[18]; Pet. Ex. 30;[19] Pet. Ex. 31.[20]

To support his opinions, Dr. Steinman relied on his expertise in MS, that 10-30% of patients with MS present with an initial attack of optic neuritis, and his own studies in which mice were caused to develop experimental encephalomyelitis ("EAE"). Pet. Ex. 15 at 9; Pet. Ex. 31[21] at 1. He explained that the optic nerve has more MOG than other place in the central nervous system

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[15] Joachim Havla et al., *Myelin-oligodendrocyte-glycoprotein (MOG) autoantibodies as potential markers of severe optic neuritis and subclinical retinal axonal degeneration*, 264 J. NEUROLOGY 139 (2017), filed as "Pet. Ex. 26."
[16] Scott S. Zamvil & Anthony J. Slavin, *Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder?*, 2(1) NEUROLOGY NEUROIMMUNOLOGY NEUROINFLAMMATION e62 (2015), filed as "Pet. Ex. 27."
[17] K. Rostásy et al., *Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica*, 19 MULTIPLE SCLEROSIS J. 1052 (2012), filed as "Pet. Ex. 28."
[18] Sharon A. Sagan et al., *Tolerance checkpoint bypass permits emergence of pathogenic T cells to neuromyelitis optica autoantigen aquaporin-4*, 113 PROC. NAT'L ACAD. SCI. 14781 (2016), filed as "Pet. Ex. 29."
[19] Sellebjerg et al., *supra* note 8.
[20] Lawrence Steinman, *Optic Neuritis, A New Variant of Experimental Encephalomyelitis, A Durable Model for All Seasons, Now In Its Seventieth Year*, 197 J. EXPERIMENTAL MED. 1065 (2003), filed as "Pet. Ex. 31."
[21] *Id*.

("CNS") and immunizing transgenic mice with MOG35-55 plus pertussis toxin can cause optic neuritis and inflammation elsewhere in the CNS. *Id*. at 9-10; Pet. Ex. 31 at 4.

The foregoing formed the basis for Dr. Steinman's theory that molecular mimics to MOG, MBP, and PLP in the Cervarix vaccine can cause or trigger optic neuritis. Pet. Ex. 15 at 10; Pet. Ex. 32.[22] Dr. Steinman pointed to the diagrams contained in his 1993 article in Scientific American to describe how shared structures on a virus, bacteria, or vaccine can trigger a cross-reactive response to self. Pet. Ex. 15 at 10 (citing Pet. Ex. 25[23]).

Utilizing BLAST searches through the protein databases of the National Library of Medicine, he looked for meaningful molecular mimics or homologies between the components of the Cervarix vaccine and MBP, PLP, and MOG. Pet. Ex. 15 at 11-12. He relied on three peer reviewed papers by *Gautam* which showed that five out of 12 amino acids, even if not consecutive, are sufficient to trigger EAE in animal studies. Pet. Ex. 15 at 13; Pet. Ex. 33[24]; Pet. Ex. 34[25]; Pet. Ex. 35.[26] Specifically, five of 11 identical amino acids between a virus and MBP, with only three being consecutive, was sufficient to induce EAE. Pet. Ex. 15 at 13-14; Pet. Ex. 35.[27] Six of 11 amino acid peptides were sufficient to trigger neuroinflammation, and four of 11 amino acids were sufficient to induce neuroinflammation "as frequently as a native 11 amino acid myelin peptide." Pet. Ex. 15 at 14; Pet. Ex. 34[28]; Pet. Ex. 33.[29]

Dr. Steinman's BLAST searches of the Cervarix HPV16 and HPV18 L1 capsid proteins and MBP, PLP, and MOG respectively found the following: HPV16 L1 and MOG resulted in a sequence of six of ten identical amino acids in a stretch of ten, and five of 12 identical amino acids in a stretch of ten in another sequence, with both fulfilling the criteria set forth in the literature as capable of triggering neuroinflammatory disease. Pet. Ex. 15 at 15-16. One sequence did not meet the criteria due to a gap in the sequence. *Id*. at 16. A BLAST search of HPV18 L1 and MOG found a sequence of five of eight identical amino acids that fulfilled the criteria for the induction of inflammation. *Id*. at 16-17. A BLAST search of HPV16 and PLP found six of 11 identical amino acids fulfilling the criteria for induction of clinical neuroinflammation. *Id*. at 17-18. A BLAST search of HPV18 and PLP found five of nine identical amino acids fulfilling the criteria. *Id*. at 18-19. A BLAST search of HPV18 L1 and MBP found no sequences that fulfilled the criteria. *Id.* at 19.

Dr. Steinman submitted that his theory is based on the results of experimental animal testing, which has been published in highly regarded peer-reviewed journals. He explained that a

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[22] GlaxoSmithKline, *supra* note 6.
[23] Lawrence Steinman, *Autoimmune Disease*, SCIENTIFIC AMERICAN, Sept. 1993, at 107, filed as "Pet. Ex. 25."
[24] Anand M. Gautam et al., *A Polyalanine Peptide with only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis*, 176 J. EXPERIMENTAL MED. 605 (1992), filed as "Pet. Ex. 33."
[25] Anand M. Gautam et al., *Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: Implications in induction of autoimmunity*, 91 IMMUNOLOGY 767 (1994), filed as "Pet. Ex. 34."
[26] Anand M. Gautam et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J. IMMUNOLOGY 60 (1998), filed as "Pet. Ex. 35."
[27] *Id.*
[28] Gautam et al., *supra* note 25.
[29] Gautam et al., *supra* note 24.

positive search is neither guaranteed nor always attained, but is not by chance. Pet. Ex. 15 at 20; Pet. Ex. 36.[30] He agreed that experiments on mice use Freund's adjuvant, a powerful additive. However, in *Ufret-Vincenty*, the scientists at NIH showed that mimicry between a virus and MBP can lead to clinical paralysis in animals by transferring T cells that cross-react with MBP and HPV: "[t]he recipients of cells that were primed with the papillomavirus peptide and stimulated in vitro with MBP developed severe relapsing-remitting EAE with an incidence of 100%". Pet. Ex. 15 at 20; Pet. Ex. 36[31]; Pet. Ex. 37.[32]

Dr. Steinman acknowledged that T cells reactive to MBP can be detected in the peripheral and central nervous systems of both healthy humans and those with MS, but this alone is insufficient for disease. Genetic and environmental factors are required before self-reactive immune responses to myelin may trigger autoimmune conditions like optic neuritis. However, molecular mimicry is the key mechanism. Pet. Ex. 15 at 22; Pet. Ex. 38[33]; Pet. Ex. 39.[34]

Dr. Steinman noted that petitioner received the third dose of Cervarix on March 20, 2014, and presented to the pediatrician on May 5, 2014, with a one-week history of severe frontal headaches. Ultimately, an MRI confirmed that she had optic neuritis with no lesions on the brain suggestive of a demyelinating disorder. Petitioner's onset was around early May, or six to seven weeks after the Cervavix vaccine, which is consistent with the onset of neuromyelitis optica ("NMO")[35] following Gardasil vaccine. Pet. Ex. 15 at 24; Pet. Ex. 40.[36]

In his supplemental report, Dr. Steinman addressed the opinions of respondent's experts, Drs. Lotze and Whitton, as well as some questions raised by the Court. Pet. Ex. 41.

Dr. Lotze agreed that petitioner had optic neuritis and placed onset on April 28, 2014, 38 days or six weeks post-vaccination, with the development of headaches that evolved into typical features of optic neuritis by May 3, 2014, including eye pain and blurred vision of the right eye. Pet. Ex. 41 at 1. Dr. Lotze argued that 38 days was too long for petitioner's optic neuritis to be associated with the Cervarix vaccine, relying on data contained in the Cervarix package insert showing the adverse event of headache to be within 7 to 30 days following vaccination. *Id*. at 2-3; Pet. Ex. 32 at 7. Dr. Steinman argued that the control group in the studies providing the data contained in the package insert received only one component of the adjuvant used in the actual vaccine, making the comparison faulty. *Id*. at 3.

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[30] Andre Silvanovich et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity*, 90 TOXICOLOGICAL SCI. 252 (2006), filed as "Pet. Ex. 36" and "Resp. Ex. C, Tab 1."

[31] *Id*.

[32] Rafael L. Ufret-Vincenty et al., *In Vivo Survival of Viral Antigen-specific T Cells that Induce Experimental Autoimmune Encephalomyelitis*, 188 J. EXPERIMENTAL MED. 1725 (1998), filed as "Pet. Ex. 37."

[33] Kohei Ota et al., *T-cell recognition of an immune-dominant myelin basic protein epitope in multiple sclerosis*, 346 NATURE 183 (1990), filed as "Pet. Ex. 38."

[34] M. Pette et al., *Myelin basic protein-specific T lymphocyte lines from MS patients and healthy individuals*, 40 NEUROLOGY 1770 (1990), filed as "Pet. Ex. 39."

[35] Neuromyelitis optica is "combined, but not usually clinically simultaneous, demyelination of the optic nerve and the spinal cord; it is marked by diminution of vision and possibly blindness, flaccid paralysis of the extremities, and sensory and genitourinary disturbances." *Neuromyelitis optica*, DORLAND'S 1249.

[36] Til Menge et al., *Neuromyelitis Optica Following Human Papillomavirus Vaccination*, 79 NEUROLOGY 295 (2012), filed as "Pet. Ex. 40."

Dr. Steinman argued that the best peer-reviewed literature he could find on timing involved the quadrivalent HPV vaccine and the onset of NMO, where the vaccine was suggested to be the putative trigger. He did not find any articles to suggest that 38 days was an unreasonable timeframe for HPV vaccination and optic neuritis. Pet. Ex. 41 at 4; Pet. Ex. 39.[37] Further, *Baxter* showed 4 cases of optic neuritis out of 1 million doses of the quadrivalent HPV vaccine occurring within 2-42 days of vaccination. Pet. Ex. 41 at 5; Pet. Ex. 42.[38]

In addressing Dr. Whitton's criticisms, Dr. Steinman argued that his theory is founded on peer-reviewed literature authored with his colleague, Dr. Gautam, BLAST searches, and an additional filtration system, the Immune Epitope Database ("IEDB"): "[t]hese papers…were used as a gating criterion to indicate there are some components of Cervarix that have a sufficient degree of identity with known areas of alignment in the BLAST search to potentially trigger autoimmune disease." Pet. Ex. 41 at 9; Pet. Ex. 33[39]; Pet. Ex. 34[40]; Pet. Ex. 35.[41] The "filtration system" uses the IEDB, a U.S. government database that catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animals in the context of infectious disease, allergy, autoimmunity, and transplantation. It also hosts tools to assist in the prediction and analysis of epitopes. Pet. Ex. 41 at 10. Dr. Steinman added that his search also found alpha-papilloavirus-9, a known epitope of the L1 major capsid protein, and L4, a monoclonal antibody that binds the HPV16 VLP found in the Cervarix vaccine. *Id*. at 11-13. Succinctly, these searches pointed to critical regions of the appropriate HPV L1 proteins in the Cervarix vaccine that are cross-reactive with antigens that are attacked in optic neuritis patients. *Id*. at 13.

Dr. Steinman acknowledged that large studies support the safety of HPV vaccines, but that does not mean the vaccine is perfect. Pet. Ex. 41 at 13; Pet. Ex. 42.[42] Rare optic neuritis has been reported after the quadrivalent HPV vaccine, and even though Cervarix is a bivalent vaccine, this is the best evidence available. Pet. Ex. 41 at 13. Dr. Steinman further acknowledged that his searches are not perfect and without "certainty," but they do provide a strong foundation for demonstrating how a molecular mimic in the Cervarix vaccine with a component of myelin known to be attacked in the optic nerve can trigger optic neuritis. *Id*. at 14.

2. Dr. Steinman's Testimony

Dr. Steinman stated "by the preponderance of the evidence," petitioner's optic neuritis was caused by the Cervarix vaccine. Tr. 28, 37. His theory involves whether any of the components of the Cervarix vaccine triggered an immune response to anything known to be attacked in optic neuritis via molecular mimicry. Tr. 41-42.

Dr. Steinman stated that optic neuritis is a rare disease often seen in MS patients. He has treated hundreds of patients with optic neuritis. Tr. 33-35. Optic neuritis involves an immune attack on the insulation or myelin on the optic nerve, affecting the axons or electrical cables that allow

[37] Pette et al., *supra* note 34.
[38] Baxter et al., *supra* note 9.
[39] Gautam et al, *supra* note 24.
[40] Gautam et al, *supra* note 25.
[41] Gautam et al, *supra* note 26.
[42] Baxter et al., *supra* note 9.

the eye to broadcast what the retina sees. Light comes into the eye and goes through the retina, information is collected, and signals are sent down the optic nerve to the brain. Interference affects vision. Tr. 33, 36. Optic neuritis can be acquired or triggered by a virus or bacteria. Tr. 36-37.

He explained that "cross-reactivity" occurs when an immune response to one thing causes an immune response to something that may not have been expected due to a common chemical structure between substance A and substance B. Tr. 47. Autoimmunity results when the immune system attacks itself as a result of a shared structure. Molecular mimicry is one of the ways this occurs and is what his theory is based on in this case. Tr. 37, 47-48.

Dr. Steinman conducted bioinformatic or BLAST computer searches to determine whether a resemblance or homology exists between the content of the Cervarix vaccine and any of the myelin protein in the white matter of the optic nerve and whether those similarities could potentially cause an immune attack. Tr. 29-30. He then added an additional search of U.S. government-funded databases to see if others had looked at what his bioinformatic searches revealed. Tr. 29. Dr. Steinman conceded that BLAST searches were not developed for the purposes that he uses them. Tr. 31.

Dr. Steinman explained that the immune system only recognizes smaller portions of a protein or six to 20 amino acids, not the whole protein. Tr. 30, 49; Pet. Ex. 15 at 15-20. Humans have an HLA molecule that has a "pocket" that can accommodate about six to 20 amino acids. This is the initial step of the immune system recognizing a large protein. Tr. 49. The "cartoon" contained in his first report shows how T cells, a component of the immune system, recognize a piece of the protein in the HLA pocket and "the concept of molecular mimicry comes alive." Tr. 50; Pet. Ex. 15 at 10.

He stated that the Cervarix vaccine contains HPV types 16 and 18, which are viral like particles ("VLP") from two strains of HPV, and adjuvants used to make the vaccine more immunogenic. Tr. 41, 54-55. The adjuvant contains AS04, which has a lipid abbreviated as MPL (3-0-desacyl-4'-monophosphoryl lipid), that is adsorbed to aluminum as the hydroxide salt. Tr. 41, 53-54; Pet. Ex. 15 at 11. The myelin sheath of the optic nerve contains MOG, PLP, and MBP. Tr. 52-53.

His BLAST searches looked for similarities between the components of the vaccine, what can be potentially attacked in optic neuritis, and how many amino acids would need to be identical in a stretch of amino acids for that to occur. He cited to *Gautam* and other studies in which he was involved to show that five out of 11 or 12 amino acids have been deemed sufficient to paralyze or produce clinically evident neuroinflammation in a standard mouse model for MS. Tr. 44, 51; Pet.

Ex. 33[43]; Pet. Ex. 34[44]; Pet. Ex. 35[45]; Pet. Ex. 47[46]; Pet. Ex. 48[47]; Pet. Ex. 49.[48] He then used the IEDB to explore if anyone had tested the sequence containing the epitopes he found. Tr. 42, 44; Pet. Ex. 47[49] at Tables 1, 4.

When conducting his BLAST searches, Dr. Steinman compared HPV16 and HPV18 of the Cervarix vaccine with MOG, PLP, and MBP found on the myelin sheath of the optic nerve. Tr. 28, 56; Pet. Ex. 15 at 16. The search of HPV18 and MOG found five of eight identical amino acids. Tr. 61. The search of HPV16 and PLP showed six of 11 identical amino acids. The search of HPV18 and PLP showed five of nine identical amino acids. However, the search of HPV18 and MBP found no sequences that met the criteria, so MBP was excluded from his analysis. Tr. 56-57, 62; *see* Pet. Ex. 15 at 15-19. Based on the *Gautam* papers, the search results identified similarities sufficient to cause an immune response causing optic neuritis. Tr. 60-61; Pet. Ex. 33[50]; Pet. Ex. 34[51]; Pet. Ex. 35.[52] He then used the IEDB to see if anyone else found what he had found, and then "took it up another notch" by searching the literature before writing his report. He stated he found the *Christensen* paper which identified monoclonal antibodies that "honed in" on HPV16 and HPV18. Tr. 57; Pet. Ex. 47.[53]

He added that his own studies show how molecular mimicry between components of the Cervarix vaccine and the proteins of the optic nerve can cause optic neuritis. Tr. 39-40; Pet. Ex. 47[54]; Pet. Ex. 48[55]; Pet. Ex. 49.[56] As further proof that molecular mimicry is still a viable and recognized mechanism for an adverse immune response, he discussed two recently published papers showing compelling data between parts of Epstein Barr virus ("EBV") or EBNA-1 resembling a protein in the myelin sheath with five of 12 identical amino acids in a stretch as a trigger for MS. Tr. 43-46; Pet. Ex. 48[57]; Pet. Ex. 49.[58] These studies support molecular mimicry as an accepted mechanism and the foundation for the theory he has held for a decade in the Vaccine Program that once you find a molecular mimic of at least five amino acids, those mimics could be immunogenic. Tr 46-47, 51; Pet. Ex. 47[59]; Pet. Ex. 48[60]; Pet. Ex. 49.[61]

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[43] Gautam et al., *supra* note 24.
[44] Gautam et al., *supra* note 25.
[45] Gautam et al., *supra* note 26.
[46] Neil D. Christensen et al., *Surface Conformational and Linear Epitopes on HPV-16 and HPV-18 L1 Virus-like Particles as Defined by Monoclonal Antibodies*, 223 VIROLOGY 174 (1996), filed as "Pet. Ex. 47."
[47] Tobias V. Lanz et al., *Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM*, NATURE (Jan. 24, 2022), filed as "Pet. Ex. 48."
[48] William H. Robinson & Lawrence Steinman, *Epstein-Barr virus and multiple sclerosis*, SCIENCE (Jan. 13, 2022), filed as "Pet. Ex. 49."
[49] Christensen et al., *supra* note 46.
[50] Gautam et al., *supra* note 24.
[51] Gautam et al., *supra* note 25.
[52] Gautam et al., *supra* note 26.
[53] Christensen et al., *supra* note 46.
[54] *Id*.
[55] Lanz et al., *supra* note 47.
[56] Robinson & Steinman, *supra* note 48.
[57] Lanz et al., *supra* note 47.
[58] Robinson & Steinman, *supra* note 48.
[59] Christensen et al., *supra* note 46.
[60] Lanz et al., *supra* note 47.
[61] Robinson & Steinman, *supra* note 48.

According to Dr. Steinman, in a perfect world, it would be possible to pinpoint the exact sequence that caused petitioner's optic neuritis if specimens could have been taken from petitioner prior to her receipt of the Cervarix vaccine. Tr. 62. The next best thing is done through bioinformatic searches with a certain amount of rigor and filtration to show what areas in the vaccine are mimics of antigens that could be attacked in optic neuritis. Tr. 63. Scientific proof exists that the human proteins MOG and PLP are linked to the development of optic neuritis, and Cervarix contains proteins that look like MOG and PLP. Tr. 63-64. Therefore, the proteins in Cervarix along with the lipid-based adjuvant were the substantial factor in petitioner's development of optic neuritis. Tr. 64.

Dr. Steinman responded to the lack of epidemiology between Cervarix vaccine and optic neuritis. Tr. 64-65. He stated that *Baxter* was a large-scale study looking at HPV-4, Gardasil vaccine, and optic neuritis. It concluded that the vaccine was "very safe, but not perfect," because there were four cases of optic neuritis out of a million doses based on the epidemiology when compared to not receiving the vaccine. Tr. 65-66; Pet. Ex. 42.[62] Dr. Steinman stated that epidemiologic studies rarely use the word causation unless it's something like smoking causes cancer. He would not expect a statement that HPV caused optic neuritis, because that is not what epidemiology is intended to do. Tr. 66-67. There are often many contributing factors in causation. While epidemiology can say that A is related to B with a high probability and what the probability and caveats are, the term causation is not used. Tr. 67.

As for timing, Dr. Steinman stated that petitioner was healthy and developed optic neuritis within 38 days of the third Cervarix vaccine with week-long frontal headaches that triggered a medical visit in early May. Tr. 31, 68, 154. According to Dr. Steinman, a neuroinflammatory response can "get revved up" in one to two days, but large-scale studies show a window of a couple of days and up to ten weeks between a vaccine and a known neuroinflammatory condition. Here, it was six to seven weeks, and the science therefore supports the onset period. Tr. 69, 154. *Baxter* used a 2 to 42-day interval in studying optic neuritis after both the Tdap and HPV vaccines. Tr. 149-50. Dr. Steinman stated that "two to 42 days seems like friendly turf for just about any vaccine-related case" that he has seen. Tr. 151. He conceded the data is minimal and that there is a disparity between the number of Tdap patients and HPV patients in the *Baxter* study, but the point was still made. Tr. 151-52.; Pet. Ex. 32.[63] Dr. Steinman agreed that *Baxter* concluded there was no increased risk of optic neuritis in the four to six weeks after vaccination but argued that the conclusion does not fit the data in Table 1 of the paper and therefore cannot be reconciled. Tr. 162-63; Pet. Ex. 42.[64]

Further, he offered the *Menge* paper, which discussed Gardasil vaccine and four cases of NMO with onset within the six-to-seven-week timeframe as support for the timeframe associated with various vaccines and neuroinflammatory conditions. Tr. 69-70; Pet. Ex. 40.[65] He added that the six-to-seven-weeks is within the 2-42-day timeframe established by epidemiologists Dr. Shoenberger and Dr. Langmuir as an acceptable interval between a vaccine and a potential injury, specifically Guillain-Barré Syndrome ("GBS"). Tr. 70-71. He stated he was not going to try to fit

[62] Baxter et al., *supra* note 9.
[63] GlaxoSmithKline, *supra* note 6.
[64] Baxter et al., *supra* note 9.
[65] *Id.*

it into a box other than to say that based on the literature provided, it was within a medically appropriate timeframe for onset. Tr. 155. While imperfect because it is a different vaccine and a different disease, the best he can do is rely on Shoenberger and the *Menge* paper on NMO. He acknowledged that petitioner did not have NMO. Tr. 155-56; Pet. Ex. 40.[66]

Dr. Steinman agreed that idiopathic optic neuritis is more common than vaccine-related optic neuritis, but the specifics of idiopathic cases are unknown due to the rarity of the condition and because the cause is often not realized or focused on in practice. Tr. 153-54. He would not call petitioner's optic neuritis idiopathic because the vaccine was a known factor that could cause optic neuritis and saying the vaccine "could cause" her optic neuritis in this context is better than saying "I don't know" what caused it. Tr. 159.

Dr. Steinman concluded that petitioner suffered a common presentation of optic neuritis, with headache, pain behind the eye, and vision loss. Tr. 36. There was no evidence of viral or bacterial infection; therefore, in his opinion, the vaccine was the trigger. Tr. 36-37. She has permanent damage to her peripheral vision and a one in five chance of developing MS. Tr. 32. Based on his experience in over 42 years of practice, the anxiety of what will happen next is one of the biggest burdens patients carry. Tr. 34. However, the longer one goes without an episode of optic neuritis, the less likely one is to develop any significant illness from it, but time is not necessarily a reassuring factor because there are sometimes long intervals between episodes. Tr. 75.

B. Respondent's Experts, Dr. Timothy Lotze & Dr. Lindsey Whitton

1. Dr. Lotze's Reports

Dr. Lotze described optic neuritis as an acquired inflammatory demyelinating syndrome of the optic nerve with abrupt onset of painful vision loss in one or both eyes. Resp. Ex. A at 3; Resp. Ex. A, Tab 1.[67] The diagnosis is based on clinical history, neurological examination, and diagnostic studies, which include MRI and cerebral spinal fluid testing. Acute optic neuritis may occur in the setting of other immune-mediated diseases including MS or NMO, but it is referred to as idiopathic optic neuritis in the absence of evidence of such chronic diseases because there is no definitive pre-disposing condition evident. Resp. Ex. A at 3. Optic neuritis develops idiopathically in 0.2 per 100,000 children, and 13 to 36% of children with optic neuritis are eventually diagnosed with MS, though the risk is higher in those with white matter lesions in other areas of the brain on MRI. In the absence of lesions, conversion to MS is uncommon. *Id*. High-dose corticosteroids typically halt the progression of inflammation and hasten recovery. Most patients with idiopathic optic neuritis have a complete recovery of their vision with no residual deficit, and recurrence is uncommon unless antibodies including those related to NMO are identified in the serum. Recent studies suggest that MOG antibodies may be a biomarker for risk of recurrent disease when persistently elevated. *Id*.

In Dr. Lotze's opinion, petitioner had idiopathic acute optic neuritis with no evidence or risk for chronic immune-mediated disease of the central nervous system. Resp. Ex. A at 4. She

[66] Menge et al., *supra* note 36.
[67] E. Ann Yeh et al., *Pediatric optic neuritis*, 87 NEUROLOGY S53 (2016), filed as "Resp. Ex. A, Tab 1."

recovered from the event with no indication of any ongoing concerns or persistent symptoms. *Id*. Further, petitioner's headache occurred more than 30 days after the vaccination and therefore was unrelated to the vaccine, based on the Cervarix package insert which states headache within seven to 30 days after vaccination. *Id*. The package insert also indicates that when compared to those receiving Cervarix, some proportion of those who received a placebo also reported headache within 30 days. *Id*. at 4-6; Pet. Ex. 32[68] at 7.

Dr. Lotze further relied on the Cervarix package insert to show that the data for New Onset Autoimmune Diseases three years after vaccination had the same potential in the group receiving Cervarix as in the control group. The package insert noted that the incidence was also the same among those receiving Cervarix vaccine and those receiving the hepatitis A vaccine in another large, randomized study. Resp. Ex. A at 6; Pet. Ex. 32[69]. The autoimmune conditions in the analysis included optic neuritis, MS, and transverse myelitis ("TM"). No association was shown between the vaccine and optic neuritis. *Id*. at 6-7.

Dr. Lotze referred to Dr. Steinman's theory as an "untested hypothesis" with no in vitro or in vivo publications to show that any sequences of the L1 capsid protein from HPV16 or HPV18 is able to induce immune cells to activate against the CNS. Resp. Ex. A at 7.

Dr. Lotze criticized the literature relied on by Dr. Steinman and his assertion that when recipient cells were primed with papillomavirus peptide and stimulated in vitro with MBP, the animals developed severe relapsing remitting EAE at an incidence of 100%, because the study used the L2 capsid antigen of HPV7. Resp. Ex. A at 7-8; Pet. Ex. 37.[70] HPV7 is associated with skin warts and mouth papillomas and is not carcinogenic. Dr. Lotze stressed that the proteins involved in the 170 different types of HPV are not interchangeable. Therefore, Dr. Steinman's statement is misleading in suggesting that all types of HPV would produce this result. Resp. Ex. A at 7-8.

Dr. Lotze further argued that the identification of sequence homologies alone is insufficient to prove cause and effect in inducing acquired demyelinating disease. He submitted an example of the development of glatiramer acetate, a synthetic copolymer used to treat MS. The initial assumption was that the copolymer would induce EAE because it had similar structural homology with MBP, but the opposite occurred, and the copolymer showed high efficacy in suppressing the incidence and severity of EAE. Resp. Ex. A at 8.

Dr. Lotze noted that Dr. Steinman agreed that *Sridhar* found no conclusive link between HPV vaccination and optic neuritis but claimed the study had many limitations in the methodology used. Resp. Ex. A at 8; Pet. Ex. 24.[71] To the contrary, Dr. Lotze stated that many large cohort studies have confirmed the findings in *Sridhar* that there is no increased risk of autoimmune diseases including optic neuritis following the quadrivalent and bivalent HPV vaccines, which include the HPV16 and 18 L1 capsid antigen. Resp. Ex. A at 8. Dr. Lotze pointed out that large studies utilize a self-controlled case series method ideal for vaccine studies because they create

[68] GlaxoSmithKline, *supra* note 6.
[69] *Id*.
[70] Ufret-Vincenty et al., *supra* note 32.
[71] Sridhar et al., *supra* note 3.

their own controls and their follow-up time can be divided into "exposed" and "unexposed" intervals: "[t]he exposed time intervals . . . relate to periods post-vaccination that are biologically attributable to the effects of the vaccine, and the unexposed follow-up represents the time intervals preceding the vaccine as well as those intervals following the exposure risk window." *Id*.

In detailing several large studies, Dr. Lotze highlighted that no increase was found in autoimmune conditions following the HPV4 vaccine. Resp. Ex. A at 9-13. He discussed a 2018 Canadian study which used a validation algorithm to assure appropriate diagnosis of various autoimmune conditions in the cohort, offering an advantage in methodology over the *Sridhar* study cited by Dr. Steinman. *Id*. at 9; Resp. Ex. A, Tab 3.[72] The results showed no increased incidence of any autoimmune condition in the 7-60 days after HPV4 vaccination and, specifically, no increased risk of optic neuritis. Resp. Ex. A at 10.

Three additional large-scale studies from Denmark, Sweden, and France found no increased risk for autoimmune disease including optic neuritis and MS in a cohort analysis after vaccination with HPV4. These studies included 997,585 girls ages 10-17 years old with a risk window period of 180 days; 3.9 million girls and women ages 10-17 years old with a 2-year risk window period analyzed by country, age, and different risk windows; and 2.2 million girls ages 13-16 years old with 12 of 14 autoimmune disorders studied following either bivalent HPV2 or quadrivalent HPV4 vaccine. Three risk windows of 0-2 months, 2-12 months, and >12 months after vaccination were studied, with no increased risk found for acquired demyelinating diseases of the central nervous system such as optic neuritis. Resp. Ex. A at 11; Resp Ex. A, Tab 4[73]; Resp. Ex. A, Tab 5[74]; Resp. Ex. A, Tab 6.[75]

A surveillance study seeking an association between HPV vaccination and central demyelinating diseases was conducted in France over a six-and-a-half-year period using a risk window of 24 months and identified no risk for central demyelination following vaccination, but rather claimed a detected protective effect from the vaccination. Resp. Ex. A at 11; Resp. Ex. A, Tab 8.[76]

Further, a case-centered analysis from Kaiser Permanente Northern California studied whether the observed rate of vaccination before onset of optic neuritis was higher than expected by comparing vaccination rates in patients with optic neuritis to those in the matched general population. Resp. Ex. A at 11; Resp. Ex. A, Tab 7.[77] During the study period, more than 20 million vaccines were administered and 179 potential cases of optic neuritis were identified after exclusion

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[72] Erin Y. Liu et al., *Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Cohort Study*, 190 CMAJ E648 (2018), filed as "Resp. Ex. A, Tab 3."

[73] Lisen Arnhein-Dahlström et al., *Autoimmune, neurological, and venous thromboembolic adverse events after immunization of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark And Sweden: cohort study*, 347 BMJ f5906 (2013), filed as "Resp. Ex. A, Tab 4."

[74] Nikolai Madrid Scheller et al., *Quadrivalent HPV Vaccination and Risk of Multiple Sclerosis and Other Demyelinating Diseases of the Central Nervous System*, 313 JAMA 54 (2015), filed as "Resp. Ex. A, Tab 5."

[75] Sara Miranda et al., *Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France*, 35 VACCINE 4761 (2017), filed as "Resp. Ex. A, Tab 6."

[76] Lamiae Grimaldi-Bensouda et al., *Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance*, 79 J. AUTOIMMUNITY 84 (2017), filed as "Resp. Ex. A, Tab 8."

[77] Baxter et al., *supra* note 9.

of patients with MS and a prior history of optic neuritis. Ninety-one cases or 51% were confirmed as optic neuritis after chart review. Case-centered analyses demonstrated no significantly increased risk of having received any vaccination, including HPV4, in the 2–42 days or 5–28 days before the onset of optic neuritis. Resp. Ex. A at 11.

Finally, a 2018 meta-analysis of the HPV vaccine and demyelinating diseases that included all the studies referenced in this case including the *Baxter* study concluded an absence of risk for optic neuritis after exposure to the HPV vaccine. Resp. Ex. A at 12; Resp. Ex. A, Tab 9.[78] "This systemic review did not find any evidence of increased risk of demyelinating event attributable to HPV vaccination . . . Therefore, the current evidence from these three sources pleads for an incidental association between vaccination and demyelination rather than a causal relationship." Resp. Ex. A at 13 (quoting Resp. Ex. A, Tab 9[79] at 8). Dr. Lotze added that the authors further suggested that the results of the study do not favor the hypothesis of molecular mimicry between the vaccine and myelin basic protein. Resp. Ex. E at 2.

Dr. Lotze argued that the data does not support Dr. Steinman's hypothesis of molecular mimicry between components of the Cervarix vaccine and myelin proteins. Resp. Ex. A at 13. Rather, the evidence is "impressive" that no association exists between HPV vaccine, demyelinating disease, and optic neuritis. *Id.*

Dr. Lotze submitted that literature discussing Gardasil and NMO is irrelevant to this case. The NMO antibody targets aquaporin-4 protein, a completely different protein from MOG, PLP, and MBP. The suggestion that the homology of aquaporin-4 IgG in the L2 capsid protein of HPV16 and HPV18 plays a role in the pathogenesis of optic neuritis is unsupported. Resp. Ex. A at 13. Additionally, NMO is a chronic relapsing disease while acute optic neuritis is a single event. Petitioner did not have NMO. Resp. Ex. E at 1.

Finally, Dr. Lotze addressed petitioner's ongoing complaints of fatigue and a persistent blind spot, arguing that a study found no increased chronic fatigue syndrome after HPV vaccination. Further, a blind spot is subjective, everyone has one where the optic nerve forms and exits the retina and is insensitive to light. Resp. Ex. A at 13; Resp. Ex. A, Tab 10.[80] Petitioner's records show a normal visual field after her recovery. Resp. Ex. A at 14. Because of the resiliency of the visual system, those who recover from optic neuritis do not report any symptoms of residual impairment, even though testing may identify subtle signs of the disease. The medical records show that petitioner was back to wearing contact lenses with no visual complaints. Resp. Ex. E at 2-3.

Dr. Lotze concluded that "no conclusive published evidence" exists to date that indicates a higher incidence of optic neuritis in association with any vaccination, including HPV. To the contrary, multiple studies evidence an absence of any association between HPV vaccination and

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[78] Julie Mouchet et al., *Human papillomavirus vaccine and demyelinating diseases—A systematic review and meta-analysis*, 132 PHARMACOLOGICAL RSCH. 108 (2018), filed as "Resp. Ex. A, Tab 9."
[79] *Id.*
[80] Berit Feiring et al., *HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway*, 35 VACCINE 4203 (2017), filed as "Resp. Ex. A, Tab 10."

optic neuritis or other acquired demyelinating diseases of the central nervous system. Resp. Ex. A at 15.

2. Dr. Lotze's Testimony

Dr. Lotze agreed that petitioner suffered from optic neuritis, but there is inadequate evidence to associate the HPV vaccine with her episode of optic neuritis. Tr. 123.

Dr. Lotze described optic neuritis as inflammation of the optic nerve, which is the large nerve that connects the eye to the brain. Inflammation and swelling disrupts the visual information to the brain and creates visual deficit. Tr. 123-24. Idiopathic optic neuritis relates to the lack of a clear trigger for the event. Acute optic neuritis generally relates to the sudden onset and rapidity of the visual change. Tr. 124. Optic neuritis is an acquired condition, and petitioner's optic neuritis was idiopathic. Tr. 140, 146.

Dr. Lotze stated that optic neuritis is associated with viruses and bacteria, as well as with other diseases such as MS, NMO, and acute disseminated encephalomyelitis ("ADEM"), none of which petitioner had. Tr. 124-25, 140. Dr. Lotze stated he would "never say never" that vaccines in general can cause optic neuritis, but one must look at the available evidence. HPV has "a very large safety margin as related to optic neuritis." Tr. 140-41. In relation to influenza vaccine, Dr. Lotze stated that the vaccine could be a consideration in some cases of optic neuritis, but the specifics of the individual patient must be considered as well. Tr. 141. He stated he was "somewhat reassured by the fact that the evidence available doesn't seem to suggest any increased incidence of optic neuritis for people who receive the HPV vaccine series." Tr. 142.

As the director of a clinic for pediatric MS and related demyelinating disorders, Dr. Lotze sees optic neuritis cases in inpatient and outpatient consultation and has treated hundreds of these patients. Tr. 125. About one third of optic neuritis cases are idiopathic. Tr. 126; Resp. Ex. A, Tab 1.[81]

In his opinion, petitioner's onset of headaches 38 days after the third Cervarix vaccine seemed unlikely to be attributable to her vaccination. Tr. 126-27. He added that the Cervarix package provides physicians with useful information, including two tables showing the potential adverse reactions that may occur within 7-30 days. It also compares Cervarix to the hepatitis A vaccine and aluminum hydroxide adjuvant. Tr. 127; Pet. Ex. 32.[82] Regarding headaches, the insert shows no statistically significant difference, with 53% of vaccine recipients versus 61% of the placebo group having a headache within seven days, and 5.3% versus 9.3% at 30 days. There was no increase in new onset autoimmune disease found related to the vaccine in the control group. Tr. 128; Pet. Ex. 32.[83]

Dr. Lotze added the reference to the onset of NMO 38 days after the quadrivalent HPV vaccine was irrelevant to this case, because NMO is a completely different disease involving aquaporin-4 protein channel antibody and petitioner was not diagnosed with NMO. Even the

[81] Yeh et al., *supra* note 67.
[82] GlaxoSmithKline, *supra* note 6.
[83] *Id.*

studies referenced with extended risk windows of up to two years did not find an increased risk for optic neuritis. Tr. 137-38.

Dr. Lotze stated that as a neurologist and based on his general knowledge, the various subtypes of HPV vary in what they may cause, with HPV16 and HPV18 causing cervical cancers and HPV7 causing common skin warts. Tr. 128-29. Dr. Steinman's reliance on a study that involved the HPV7 antigen inducing EAE in mice was irrelevant, since the L2 capsid antigen in HPV7 is not known to be carcinogenic when compared to HPV16 and HPV18. Therefore, one cannot assume the antigens are interchangeable. Tr. 129-131; Pet. Ex. 37.[84]

Dr. Lotze provided an example of glatiramer acetate, one of the older medicines used to treat MS, which was originally thought to be a trigger for EAE due to a number of amino acids it had that seemed similar to myelin proteins. However, it resulted in the opposite. Tr. 131-32; Resp. Ex. A; Resp. Ex. A, Tab 2.[85] Therefore, it cannot be assumed that sequence homologies and similarities to myelin proteins necessarily induce an autoimmune reaction. Tr. 132-133. Based on the evidence, Dr. Lotze does not believe the HPV vaccine can cause optic neuritis, because large studies and trials "with really strong methodology" have not presented strong evidence that would associate the vaccine with optic neuritis. Tr. 133.

Dr. Lotze discussed various large studies including one from Canada involving 290,000 girls ages 12 to 13 with 81% having received three doses of HPV vaccine. Various diagnoses were validated, and optic neuritis was looked at specifically. There was no increase found in autoimmune conditions within seven to 60 days after HPV vaccination. Tr. 133-34; Resp. Ex. A at 9-10; Resp. Ex. A, Tab 3.[86]

Dr. Lotze added that a French study looked for nervous system demyelinating disease up to 24 months after HPV vaccination and found no increased risk but rather suggested a protective effect from vaccination, with a lower risk of central demyelination/MS in those who were fully vaccinated. Tr. 135-36; Resp. Ex. A at 11-12; Resp. Ex. A, Tab 8.[87]

Finally, he referred to the *Mouchet* meta-analysis as particularly useful because it included all the earlier studies and showed no association between HPV vaccination and optic neuritis. Tr. 136-37; Resp. Ex. A at 12; Resp. Ex. A Tab 9.[88] He later agreed that the meta-analysis looked at GBS, MS, anaphylaxis, venous thromboembolism, and stroke, but not specifically optic neuritis. Tr. 144-45; Resp Ex. A, Tab 8[89]; Resp. Ex. A Tab 9.[90] He further agreed the Norway study he relied on looked at fatigue, not optic neuritis. Tr. 145-46; Resp. Ex. A, Tab 10.[91]

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[84] Ufret-Vincenty et al., *supra* note 32.
[85] R. Arnon & R. Aharoni, *Glatiramer Acetate: From Bench to Bed and Back, in* TRANSLATIONAL NEUROIMMUNOLOGY IN MULTIPLE SCLEROSIS (2016), filed as "Resp. Ex. A, Tab 2."
[86] Liu et al., *supra* note 72.
[87] Grimaldi-Bensouda et al., *supra* note 76.
[88] Mouchet et al., *supra* note 78.
[89] Grimaldi-Bensouda et al., *supra* note 76.
[90] Mouchet et al., *supra* note 78.
[91] Feiring et al., *supra* note 80.

Based on the package insert and the literature cited, it is Dr. Lotze's opinion that the Cervarix vaccine did not cause petitioner's optic neuritis. Tr. 137, 147. He acknowledged that most of the studies he relied on involved the Gardasil vaccine and that Gardasil and Cervarix are different products because they contain different adjuvants. However, both vaccines contain HPV16 and HPV18 L1 capsids, the two components argued in this case to be related to optic neuritis, and the studies show no association between Gardasil and optic neuritis. Tr. 142-43, 147; Resp. Ex. A, Tab 3.[92]

3. Dr. Whitton's Reports

Dr. Whitton wrote two reports and focused only on whether HPV vaccine can cause optic neuritis. Resp. Ex. C; Resp. Ex. F.

Dr. Whitton noted that the Cervarix vaccine contains L1 proteins from two strains of HPV, HPV16 and HPV18. Myelin is the substance that covers human nerves and contains three human proteins: MBP, MOG, and PLP. Dr. Steinman's mechanism of molecular mimicry involves the most common proteins and shared amino acid sequences or homologies. In trying to implicate the HPV vaccine in petitioner's optic neuritis, Dr. Steinman conducted BLAST searches finding five or more of 12 amino acids that are identical and claimed that HPV16 and HPV18 can be causative. Resp. Ex. C at 3-4.

Dr. Whitton explained that a "mimic" is the immune response that the sequence induces, not the shared homology with an amino acid sequence. The amino acid sequence must trigger an immune response and "cross react" with the peptide to be a mimic. Unless both things occur, there is no mimic, "it is merely a homology." Resp. Ex. C at 3-4. The homologies identified by Dr. Steinman from his BLAST searches do not show that they can induce an immune response, that this hypothetical response is cross-reactive, or that the "imaginary" cross reactive immune response can produce disease. *Id*. at 4. Antibodies or T cells would be present if a homology induced mimicry, but BLAST searches do not provide such evidence. While Dr. Steinman argued that antibodies and T cells are not routinely analyzed in clinical practice, Dr. Whitton argued that "homologies cannot be termed 'meaningful' until some biological effect has been demonstrated." Resp. Ex. C at 4.

According to Dr. Whitton, BLAST searches were designed to help scientists evaluate the relationships between various proteins, analyze evolutionary relationships, assign them to a family or super-family, and infer the function of a newly identified protein if its sequences were similar to those of a protein with a known function. Resp. Ex. F at 2; Pet. Ex. 44.[93] The intended purpose of BLAST was not to identify immunologically relevant short homologies, which is how Dr. Steinman is using it. The overview of BLAST does not mention "immune, epitope, vaccine, or mimicry" in its description. Resp. Ex. F at 2.

Dr. Whitton submitted that Dr. Steinman used a screen grab that shows regions of homology between two proteins he compared. However, those BLAST homologies occurred by

[92] Liu et al., *supra* note 72.
[93] Stephen F. Altschul et al., *Basic Local Alignment Search Tool*, 215 J. MOLECULAR BIOLOGY 403 (1990), filed as "Pet. Ex. 44."

chance according to Dr. Whitton. The results Dr. Steinman characterized as "negative" because the search did not display any output were not actually negative. Resp. Ex. F at 3. Rather, the expect value or "E-value" used in his searches describes the number of hits expected to be seen by chance when searching a database of a particular size. The E-value decreases as the "score" of matches increases. "Essentially, the E value describes random background noise. For example, an E value of 1 assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see 1 match with a similar score simply by chance." *Id*. Dr. Steinman frequently presents searches with an E-value of three, which means when comparing two proteins, one would expect approximately three similar homologies to occur by chance. This raises the question of what might be considered a meaningful E-value when trying to identify immunologically significant homologies. *Id*. Further, BLAST searches have a user defined expect threshold setting with the default set at ten, meaning all homologies with an E-value of ten or above will not be displayed. Therefore, using the default settings, many of the homologies identified in the BLAST search are hidden from the user, but this does not mean they do not exist. *Id*. at 3-4.

Dr. Whitton took issue with Dr. Root-Bernstein being an exemplar for Dr. Steinman's use of BLAST, arguing that Dr. Root-Bernstein used BLAST incorrectly to draw unjustified conclusions about molecular mimicry. Resp. Ex. F at 4-5; 11 Pet. Ex. 41; Pet. Ex. 45.[94]

Dr. Whitton then discussed the various homologies Dr. Steinman focused on from his BLAST searches of HPV16 and HPV18 L1 with MBP, MOG, and PLP. Resp. Ex. C at 4-5. When Dr. Whitton conducted his own search of HPV16 and MOG, he found 24 additional homologies of five out of 12 or better, where Dr. Steinman found only two "meaningful" homologies. Dr. Whitton explained this is because short homologies are commonplace and not as convincing as Dr. Steinman suggests. The existence of homology provides nothing about immune response, cross reactivity, molecular mimicry, or disease. *Id*.

Further, the existence of homology does not prove biological impact. Resp. Ex. C at 9. Dr. Whitton explained that when a foreign protein is injected into an animal, an immune response is made only to certain parts of the protein, not to every run of amino acids in the protein. A BLAST search which shows homology does not mean that homology triggers an immune response. *Id*. Proteins fold into complex three-dimensional structures with the relevant part of the protein potentially hidden inside the fold and inaccessible. Even if accessible, most homologies are imperfect, meaning many of the amino acids are different. *Id*. Therefore, one cannot assume that an immune response induced by the foreign protein will be able to recognize the homologous sequence when it differs in many of its amino acids. Further, even if this immune response occurs and is cross-reactive, it does not mean it causes disease. *Id*.

To illustrate the foregoing, Dr. Whitton searched HPV L1 and albumin, identifying 42 homologies of five out of 12 or better. If one were to apply Dr. Steinman's theory, the existence of these homologies in the HPV vaccine would mean they must trigger an immune response that

[94] Robert Root-Bernstein, *Rethinking molecular mimicry in rheumatic heart disease and autoimmune myocarditis: laminin, collagen IV, CAR, and B1AR as initial targets of disease*, 2 FRONTIERS IN PEDIATRICS 1 (2014), filed as "Pet. Ex. 45" and "Resp. Ex. F, Tab 3."

can cross-react with albumin and cause some form of molecular mimicry-based disease. However, HPV does not cause any such disease. Resp. Ex. C at 9.

Dr. Whitton argued that evidence shows that most homologies do not trigger biologically meaningful cross reactivity. Resp. Ex. C at 9. Dr. Whitton's comparisons of the proteins from HPV16 and HPV18 found 326 homologies of five out 12, five of which were perfect 12 of 12 matches. If Dr. Steinman's theory were correct, the immune responses to a given homology in the HPV16 L1 protein should "see" the related sequence in the HPV18 L1 protein. If the cross-reactive immune responses were meaningful, then the immune response against the HPV16 L1 protein should confer protection against both HPV16 and HPV18, but it does not: "[i]n reality, the L1 proteins from different strains of HPV are included in the vaccine because—despite the very large number of shared homologies—the immune response triggered by the L1 protein from one virus does not 'meaningfully' cross react with, or protect against, the other viruses." *Id*. at 10. Thus, this disproves Dr. Steinman's theory that a short homology between two proteins must inevitably induce meaningful cross reactive immune responses. *Id*. Dr. Whitton proposed that, for Dr. Steinman's theory on short homologies to be sufficient, three things had to have occurred: the homologies had to have induced an immune response that then cross-reacted with a host protein that then caused the subsequent development of petitioner's optic neuritis. Based on data, Dr. Whitton concluded that even with the 326 homologies he found, it would be wrong to conclude that even one must more likely than not have a "meaningful biological impact." *Id*.

Regarding the BLAST search of HPV18 and MBP that Dr. Steinman claimed to have a negative result, Dr. Whitton's search identified 17 homologies of five out of 12 or better. Therefore, Dr. Steinman's search was not a negative result but an appearance of a negative result due to the use of the default E-value of 10. Resp. Ex. F at 5; Pet. Ex. 41 at 9; Pet. Ex. 15 at 19-20. When Dr. Whitton left all the parameters at default but increased the E-value to 500, his search returned seven hits, with one showing five out of eight homologies. Using the default E-value of 10 prevents all the "hits" from being displayed, but this does not mean the search is "negative" as characterized by Dr. Steinman. Resp. Ex. F at 5.

Dr. Whitton relied on *Trost*, which compared bacterial proteins to the human proteome and identified "thousands" of short homologies, to show that the "'elusive character of the molecular mimicry hypothesis . . . past and present data tend to exclude a causal mechanistic role for molecular mimicry in the genesis of autoimmunity.'" Resp. Ex. C at 10; Resp. Ex. C, Tab 2.[95]

Dr. Whitton further disagreed with Dr. Steinman's interpretation of the *Ufret-Vincenty* paper, pointing out that the study discussed L2, a different HPV protein that is not present in the Cervarix vaccine. Mice were injected with a powerful adjuvant to drive the activation of peptide-specific T-cells. In the absence of pertussis toxin, which is required to allow T cells to efficiently enter the CNS, the mice did not develop CNS disease. Ten days later, the mice were sacrificed and their T cells were harvested and stimulated with a peptide in a tissue culture dish for four days, then 100 million of these highly activated T cells were injected into another mouse, who developed

[95] Brett Trost et al., *Bacterial peptides are intensively present throughout the human proteome*, 1 SELF/NONSELF 71 (2010), filed as "Resp. Ex. C, Tab 2."

EAE seven to nine days later. This is not the same as receiving a vaccination, and more generally, the study is irrelevant to the instant case. Resp. Ex. C at 11; Pet. Ex. 37.[96]

Further, large-scale studies focused mostly on the quadrivalent Gardasil vaccine, which contains both the HPV16 and HPV18 L1 proteins contained in the Cervarix vaccine, showed no increase of autoimmune disorders following the administration of millions of vaccines. Four of the studies included optic neuritis and molecular mimicry. Resp. Ex. C at 11-13. The most recent studies focused on GBS, with no solid evidence found of autoimmune neurological disease precipitated by the HPV vaccine. *Id*. at 13. Further, a 2017 study by the WHO Global Advisory Committee on Vaccine Safety reported no adverse reactions other than anaphylaxis and anxiety-related syncope following greater than 270 million doses of HPV vaccine administered worldwide, concluding that HPV vaccines were considered safe. *Id*. Based on his review of the continuing post-licensure studies of HPV vaccines, Dr. Whitton concluded "[t]here remains no convincing evidence that HPV vaccines are associated with optic neuritis or, indeed, with any autoimmune disease." Resp. Ex. C at 13.

Dr. Whitton then discussed the IEDB searches and the two articles that Dr. Steinman relied on. Resp. Ex. F at 1; Pet. Ex. 41; Pet. Ex. 44[97]; Pet. Ex. 45.[98] Dr. Whitton described Dr. Steinman's approach to BLAST and IEDB searches in extensive detail, beginning with the BLAST search of HV16 L1 and PLP. Resp. Ex. F at 6. A sequence found in this search was put into the IEDB, which located alpha-papillomavirus-9, a known L1 major capsid protein. *Id*. Next, Dr. Steinman looked to see if anyone else had tested the HPV16 sequence and found that the sequence DVNVYHIFFQMSLWLPSEAT is an epitope. Dr. Steinman wrote "[t]he monoclonal L4 binds the HPV16 VLP, found in the Cervarix vaccine," and "[t]his epitope contains the cross-reactive epitope to PLP that the antibody recognizes." *Id*.; Pet. Ex. 41 at 11-13. Dr. Steinman then concluded that the filtration process showed critical regions of the appropriate HPV L1 proteins in the Cervarix vaccine and "[t]hese regions are cross-reactive with antigens that are actually attacked in optic neuritis patients." *Id.*

Dr. Whitton detailed the various steps described above and summarized that all Dr. Steinman did was take a peptide from HPV L1 and use the IEDB to show that the peptide partially overlaps with the known epitope. This does not show cross reactivity with the antigens attacked in optic neuritis. Resp. Ex. F at 6-11; Pet. 41 at 14.

Dr. Whitton concluded that Dr. Steinman's BLAST searches contain many flaws and were used improperly. The use of the IEDB filter funnel added no significant value to his findings, and the observation of partial overlap between BLAST homology and IEDB epitope carries no weight because both the homology and the overlap are "demonstrably the results of chance." Resp. Ex. F at 11-12.

[96] Ufret-Vincenty et al., *supra* note 32.
[97] Altschul et al., *supra* note 93.
[98] Root-Bernstein, *supra* note 94.

4. Dr. Whitton's Testimony

Dr. Whitton stated that the theory in this case is that one of the L1 proteins in the Cervarix vaccine triggered a process called molecular mimicry which led to petitioner's development of optic neuritis. Tr. 78. Dr. Whitton agreed that petitioner suffered from optic neuritis, but stated the Cervarix vaccine did not play a causal role in her development of optic neuritis. Tr. 79-80.

Dr. Whitton has published several papers on molecular mimicry. He defined molecular mimicry as having two basic steps: one, a foreign material must first induce an adaptive immune response of T cells or antibodies, and two, the adaptive immune response must be able to see or cross-react with one of the body's own proteins. Both steps must occur to have molecular mimicry and, theoretically, lead to disease. Tr. 80-81. However, it is not "inevitable" that disease will occur, because healthy people have autoreactive responses that are not harmful. Tr. 81.

Dr. Whitton agreed that Cervarix is designed to elicit an adaptive immune response. Tr. 100. He did not know if the AS04 adjuvant used in Cervarix was new at the time but explained that adjuvants are used in non-live vaccines to induce good T cell response, specifically CD4 T cell response. Tr. 102.

As detailed in his first report, BLAST searches were initially designed to help scientists evaluate relationships between various proteins and to analyze evolutionary relationships to show that proteins belonged to the immunoglobulin family, or to the immunoglobin super family, which is a broader class of proteins. It "was not designed for immunological purposes." Tr. 82; Resp. Ex. F at 2.

Dr. Whitton described the BLAST search conducted by Dr. Steinman comparing the HPV L1 sequence present in Cervarix to a protein Dr. Steinman believes may be relevant in optic neuritis. Three results were found that would be called "homology." Tr. 82-84; Pet. Ex. 15 at 16. He explained that homology refers to where there are aligned sequences between two different proteins. Both the vaccine and the host protein contain amino acid C, for cysteine, at position one. Tr. 84; Pet. Ex. 15 at 16. However, homologies are "astonishingly common." If one compares two proteins of decent or average length, like 400 amino acids, there will be multiple homologies. Tr. 84-85.

As for Dr. Steinman's "negative result", Dr. Whitton explained that when BLAST search comparisons of two proteins are conducted, it will display some but not all homologies, because it has a cutoff or "expect threshold." Tr. 85; Resp. Ex. F at 4; Pet. Ex. 15; Pet. Ex. 41. The BLAST expect threshold default value is 10. Assuming Dr. Steinman did not alter the threshold, the search will not show the results above the threshold of 10, but this does not mean there was a negative result, only that the results above the threshold were not displayed. Tr. 86; Resp. Ex. F at 5; Pet. Ex. 15; Pet. Ex. 41.

Dr. Whitton stated he conducted the same comparison on a different program and found 17 homologies of five out of 12. Tr. 87, 105. He then conducted a search of what Dr. Steinman claimed to be negative but changed the expect value, which only alters what the user is shown. Tr.

87-88; Resp. Ex. F at 5. This showed a homology that was not visible on Dr. Steinman's search, demonstrating that his search was not in fact negative. Tr. 87-88, 111-12.

Dr. Whitton stated that *Silvanovich* provided three messages. First, BLAST was not designed for immunological purposes, it is used to look for potential antibody cross-reactivity. Second, if BLAST is used for immunological purposes to look for antibody responses, then one should be looking for homologies that are at least 80 amino acids in length with at least 28 identical amino acids. Third, short homologies like those examined by Dr. Steinman are "basically random" and homologies of five out of 12 are found all the time when comparisons are done properly. Tr. 88-91; Resp. Ex. C, Tab 1.[99] Dr. Whitton reiterated that the mere presence of homology does not mean the vaccine will more likely than not trigger an adaptive immune response, trigger molecular mimicry, or cause disease. Tr. 91.

Dr. Whitton explained that, with every homology displayed, the BLAST algorithm returns the expect threshold, or e-value, which is the probability that the homology would occur due to chance. Using Dr. Steinman's comparison of one protein against another, the result was 0.76, meaning you could expect to find "a little less than one homology of this type every time you did that comparison." Tr. 91-92. Dr. Steinman's findings also showed an e-value of 4.0, meaning you would expect to find four homologies by random chance. Tr. 92-93; Pet. Ex. 15 at 16.

Dr. Whitton referenced a second article by *Silvanovich* that discussed the biological significance of the e-value. He summarized that the paper found that the e-value should be no higher than 3.9 times 10 to the negative 7, meaning there is one chance in 2.5 million that this is a chance homology. Tr. 93-94; Resp. Ex. F, Tab 2.[100] In comparison, Dr. Steinman's e-values are roughly 2.5, making them "about a million times too high to be considered of possible significance." Tr. 94. Succinctly, based on the e-values Dr. Whitton identified, Dr. Steinman's expert reports, and the articles filed by Dr. Whitton, there is no reason to believe that Dr. Steinman demonstrated homologies that would cause disease. Even though molecular mimicry is not all that unusual, causing disease is "pretty unusual so far as we know." Tr. 94.

Dr. Whitton commented that *Root-Bernstein* was "full of genuinely egregious errors" and "complete" mistakes. Tr. 95; Resp. Ex. F, Tab 3[101]; Pet. Ex. 45.[102] The e-threshold was set at the maximum value of 10,000, which ensured the results showed a lot of homologies which are of no biological relevance. Tr. 95-96; Resp. Ex. F, Tab 3[103] at 3. The author then tabulated sequences with e-values greater than 60, which was "the wrong thing to be doing," because you want to look at low e-values. According to Dr. Whitton, the paper is unreliable. Tr. 96.

Dr. Whitton concluded that there is no evidence that HPV vaccine causes optic neuritis. Publications have looked explicitly at the association and failed to identify any relationship. Tr. 96-97. *Scheller* studied about two million doses of HPV given to females ranging in age from 10

[99] Silvanovich et al., *supra* note 30.
[100] Andre Silvanovich et al., *The use of E-scores to determine the quality of protein alignments*, 54 REG. TOXICOLOGY & PHARMACOLOGY 526 (2009), filed as "Resp. Ex. F, Tab 2."
[101] Root-Bernstein, *supra* note 94.
[102] *Id*.
[103] *Id*.

to 44 looking for demyelinating diseases including optic neuritis and found no detectible increased risk of any of those diseases. Tr. 97; Resp. Ex. C, Tab 4.[104] The WHO published a broader paper after looking at 270 million doses of HPV vaccine and found no serious adverse events linked to the vaccine other than anaphylaxis and anxiety-related syncope. Tr. 97; Resp. Ex. C, Tab 11.[105]

On cross-examination, Dr. Whitton explained that if homologies were sufficient for a cross-reactive immune response to be induced, then the Cervarix vaccine would only need one L1 protein because the protein from HPV16 would be sufficient to protect against HPV18. Tr. 106. However, the L1 protein of one strain of HPV does not confer protection against different strains despite a vast number of homologies, which is why the vaccine contains both HPV16 and HPV18 L1 proteins. Tr. 106-07.

When pressed further, Dr. Whitton maintained his opinion that homologies are commonplace. If one accepts Dr. Steinman's argument, protein comparisons could literally be applied to any vaccine protein and any disease. Tr. 110. For example, if this were a GBS case, Dr. Steinman could take the same L1 protein from HPV and compare it with Contactin-1 and find homologies. Tr. 110. Any time there is a question of a vaccine causing a disease applying Dr. Steinman's approach will always be resulting homologies. Tr. 111.

Further, in molecular mimicry, the first two steps of inducing an adaptive immune response and cross-reactivity are not uncommon, but the third step of causing disease is very different. Tr. 113. "The father of autoimmunity in the United States, the late Dr. Noel Rose," stated "there are very few instances of molecular mimicry known to cause disease in humans; very, very few." Tr. 113. It is very easy to speculate, to show correlation, and to assume that the disease is caused by molecular mimicry, but he "strongly disagree[d]" because cross-reactive immune responses are not unusual in humans. Tr. 113.

Dr. Whitton agreed that *Science* and *Nature* are reputable journals. He read the papers on EBV virus and MS but had not "dissected" them. Tr. 114-15; Pet. Ex. 47[106]; Pet. Ex. 48[107]; Pet. Ex. 49.[108] Dr. Steinman's paper shows the presence of cross-reactive immune responses between viral protein and human protein, which is well-known. EBV has previously been associated with MS. Tr. 115; Pet. Ex. 49.[109] The other paper on EBV and MS from Harvard discussed how live viral infection can cause disease in multiple different ways, molecular mimicry being one, but there are still many other possibilities so these papers cannot be too closely equated to this case. MS is a different disease than optic neuritis, and this case involves a killed virus vaccine. Tr. 116; Pet. Ex. 48.[110] Further, those papers did not mention BLAST, so it is inappropriate to use them to validate the BLAST approach. Tr. 117. Dr. Whitton added:

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[104] Scheller et al., *supra* note 74.
[105] World Health Organization, 92 WEEKLY EPIDEMIOLOGICAL RECORD 393-404 (Jul 14, 2017), filed as "Resp. Ex. C, Tab 11."
[106] Christensen et al., *supra* note 46.
[107] Lanz et al., *supra* note 47.
[108] Robinson & Steinman, *supra* note 48.
[109] *Id*.
[110] Lanz et al., *supra* note 47.

> just to be clear . . . I do not believe for one second that the paper shows a causal linkage . . . It's showing that an antibody purified from a patient with multiple sclerosis can recognize both a short sequence of a host protein and a short sequence of a viral protein that can be called EBNA-1 . . . And I have no dispute about that. But I do not believe that that paper shows that that observation explains the development of disease.

Tr. 117-18; Pet Ex. 48.[111] He stated that short cross-reactive sequences have been known for 30 years, and the paper shows this has been linked to EBV, and a different paper has linked EBV to MS. However, "whenever you put links in a chain . . . they all need to be tested." Tr. 118; Pet. Ex. 48[112]; Pet. Ex. 49.[113]

Dr. Whitton concluded that these articles allow the inclusion of molecular mimicry as a possible mechanism by which a live viral infection causes demyelinating disease. Live viral infections can cause all kinds of disease, and the vast majority have nothing to do with molecular mimicry. Though Dr. Whitton is "very convinced that EBV is involved" in the causation of MS, it is not known how it does so. Tr. 119.

IV. Applicable Law

A. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *See Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[114]

To prove causation for an "off-Table" injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination

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[111] *Id*.
[112] *Id*.
[113] Robinson & Steinman, *supra* note 48.
[114] The Vaccine Act also requires petitioners to show by preponderant evidence the vaccinee suffered from the "residual effects or complications" of the alleged vaccine-related injury for more than six months, died from the alleged vaccine-related injury, or required inpatient hospitalization and surgical intervention as a result of the alleged vaccine-related injury. § 11(c)(1)(D). It is undisputed that this requirement is satisfied in this case.

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. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioner to provide a "reputable medical theory" demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id.* at 961 (citation omitted), and "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," *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375). Petitioner is not, however, required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of eliminating alternative independent potential causes").

To satisfy the third *Althen* prong, petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the

temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

B. Legal Standard Regarding Fact Finding

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. § 11(c)(2). Medical records created contemporaneously with the events they describe are presumed to be accurate and "complete" such that they present all relevant information on a patient's health problems. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). In making contemporaneous reports, "accuracy has an extra premium" given that the "proper treatment hang[s] in the balance." *Id.* Contemporaneous medical records that are clear, consistent, and complete warrant substantial weight "as trustworthy evidence." *Id*. Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948). But petitioners can support their claim with oral testimony if it is credible and consistent with the medical records. *See, e.g.*, *Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). In short, "the record as a whole" must be considered. § 13(a).

C. Evaluating 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 his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). 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 ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all of the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human 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 & Human 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).

V. Analysis

Because petitioner does not allege an injury listed on the Vaccine Injury Table, her claim is classified as "off-Table." As noted above, for petitioner to prevail on an "off-Table" claim, she must show by preponderant evidence that her injury resulted from the vaccination at issue. *Capizzano*, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that the injury was caused by factors unrelated to the vaccinations. *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013).

A. Althen Analysis

1. *Althen* Prong I

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 & Human 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.

For the following reasons, the undersigned finds petitioner has, by preponderant evidence, provided a sound and reliable theory that the Cervarix vaccine can cause and/or trigger optic neuritis. Therefore, petitioner has satisfied the first *Althen* prong.

Petitioner has alleged an "off-Table" injury, and thus must prove by preponderant evidence a medical theory causally connecting the Cervarix vaccine to her optic neuritis. Petitioner theorizes that the Cervarix vaccine caused or triggered her optic neuritis through molecular mimicry. The theory of molecular mimicry explains how an infection or vaccine can lead to an autoimmune disease. When a foreign antigen and an antigen produced by the body share certain attributes such as similar protein peptides or a similar structural architecture, the immune system can mistakenly attack the self-produced antigen due to its similarities with the foreign "mimic." Tr. 28, 37, 39-42;

47-48; Pet. Ex. 47[115]; Pet. Ex. 48[116]; Pet. Ex. 49.[117] A demyelinating disease is an autoimmune disease that occurs when the immune system attacks part of the body's central nervous system.

The optic nerve is part of the CNS and is surrounded by a myelin sheath that insulates the optic nerve and ensures that the electric impulses to and from the nerve are transmitted efficiently. The myelin sheath contains proteins, specifically MOG, PLP, and MBP. Tr. 33; 36-37. When the myelin sheath is damaged due to an autoimmune disease, it results in a demyelinating disease, i.e., optic neuritis. *Id.;* Resp. Ex. A at 3; Resp. Ex. A, Tab 1.[118]

Molecular mimicry has long been used and accepted as a mechanism by which vaccines can cause or trigger autoimmune diseases in the peripheral and central nervous system. Many of the articles filed in this case support the mechanism as the leading hypothesis for the etiology of autoimmune diseases involving the peripheral and central nervous system. Pet Ex. 33[119]; Pet. Ex. 34[120]; Pet. Ex. 35[121]; Pet. Ex. 47[122]; Pet. Ex. 48[123]; Pet. Ex. 49.[124] The theory has been extended from infectious agents to vaccine-associated autoimmune illnesses including GBS, TM, and optic neuritis. *See Reinhardt v. Sec'y of Health & Human Servs*., No. 17-1257V, 2021 WL 1851491 (Fed. Cl. Spec. Mstr. Apr. 2, 2021) (finding flu vaccine caused petitioner to develop optic neuritis via molecular mimicry); *Day v. Sec'y of Health & Human Servs.*, No. 12-630V, 2015 WL 8028393 (Fed. Cl. Spec. Mstr. Nov. 13, 2015) (finding Gardasil and flu vaccine led petitioner to develop neuromyelitis optica via molecular mimicry); *Salmins v. Sec'y of Health & Human Servs*., No. 11-140V, 2014 WL 1569478 (Fed. Cl. Spec. Mstr. Mar. 31, 2014) (finding HPV vaccine caused petitioner to develop GBS via molecular mimicry); *Roberts v. Sec'y of Health & Human Servs*., No. 09-427V, 2013 WL 5314698 (Fed. Cl. Spec. Mstr. Aug. 29, 2013) (finding Tdap vaccine led petitioner to develop transverse myelitis via molecular mimicry).

The Vaccine Program has accepted the theory of molecular mimicry as sound and reliable for both peripheral and central nervous system demyelinating injuries where similarities have been shown between the components in a vaccine and components on the peripheral or central nervous system utilizing bioinformation systems. That is not to say that there has been conclusive proof of causation in any of these off-table cases, but rather that sound and reliable theories supported by medical evidence have been provided. *See, e.g.*, *Conte v. Sec'y of Health & Human Servs.*, No. 17-403V, 2020 WL 5743696, at *23 (Fed. Cl. Spec. Mstr. July 27, 2020); *Barone v. Sec'y of Health & Human Servs.*, No. 11-707V, 2014 WL 6834557, at *8-9 (Fed. Cl. Spec. Mstr. Nov. 12, 2014) (noting molecular mimicry "has been accepted in other Program cases as a reliable medical explanation for how various autoimmune conditions could develop after the receipt of different kinds of vaccinations"); *Koller v. Sec'y of Health & Human Servs.*, No. 16-439V, 2021 WL 5027947, at *18 (Fed. Cl. Spec. Mstr. Oct. 8, 2021); *Pierson v. Sec'y of Health & Human Servs.*,

[115] Christensen et al., *supra* note 46.
[116] Lanz et al., *supra* note 47.
[117] Robinson & Steinman, *supra* note 48.
[118] E. Ann Yeh et al., *Pediatric optic neuritis*, 87 NEUROLOGY S53 (2016), filed as "Resp. Ex. A, Tab 1."
[119] Gautam et al., *supra* note 24.
[120] Gautam et al., *supra* note 25.
[121] Gautam et al., *supra* note 26.
[122] Christensen et al., *supra* note 46.
[123] Lanz et al., *supra* note 47.
[124] Robinson & Steinman, *supra* note 48.

No. 17-1136V, 2022 WL 322836, at *31 (Fed. Cl. Spec. Mstr. Jan. 19, 2022). *But see Deshler v. Sec'y of Health & Human Servs.*, No. 16-1070V, 2020 WL 4593162, at *19 (Fed. Cl. Spec. Mstr. July 1, 2020) (accepting molecular mimicry as generally valid but finding petitioner's specific argument unpersuasive).[125]

Dr. Steinman testified that the Cervarix vaccination petitioner received contained components that share similar structures or sequences with components of the myelin sheath, which could trigger an autoimmune response capable of damaging petitioner's optic nerve. Tr. 47-48. Specifically, the peptide sequences of the HPV16 L1 and HPV18 L1 in the Cervarix vaccine are similar to and can mimic the components of the myelin sheath—MOG, PLP, and/or MBP. Pet. Ex. 15 at 9; Pet. Ex. 26[126]; Pet. Ex. 27[127]; Pet. Ex. 28[128]; Pet. Ex. 29[129]; Pet. Ex. 30[130]; Pet. Ex. 31.[131] Dr. Steinman acknowledged that genetic and environmental factors are required before self-reactive immune responses to myelin may trigger autoimmune conditions like optic neuritis; however, molecular mimicry is the key mechanism. Pet. Ex. 15 at 22; Pet. Ex. 38[132]; Pet. Ex. 39.[133]

Dr. Steinman cited three papers by *Gautam* which show that 5 of 12 amino acids are sufficient to reliably produce clinically evident inflammation in a mouse. Pet. Ex. 33[134]; Pet. Ex. 34[135]; Pet. Ex. 35.[136] He explained that since human specimens cannot be secured, the exact sequence that caused optic neuritis cannot be pinpointed. Tr. 62. The best that can be done is bioinformatic searches with a certain amount of rigor and filtration to show what areas in the vaccines are mimics of antigens that could be attacked in the purported injury. Tr. 29-30, 49, 63; Pet. Ex. 15 at 10, 13-14. He conducted BLAST searches that showed five of eight identical amino acids when comparing HPV18 L1 and MOG; five of nine identical amino acids when comparing HPV18 L1 and PLP; and six of 11 identical amino acids when comparing HPV16 L1 and PLP. No sequences were found when comparing HPV18 L1 and MBP. Tr. 52-53; 56, 61-62; Pet. Ex. 15 at 8-9, 16. Dr. Steinman concluded that the components of the vaccine had "identities of interest based on the *Gautam* papers, and an immune response to those regions could well precipitate optic neuritis." Tr. 51, 56-57, 60-61; Pet. Ex. 15 at 16. He then took it further through IEDB searches. Tr. 42-44; Pet. Ex. 47[137] at Table 1, 4.

Dr. Steinman's theory of molecular mimicry is not new, he has been using it in the Program for a decade to explain how a vaccine could cause disease. However, he has now added two newly published papers to bolster the continued viability of molecular mimicry as a mechanism for autoimmunity when there is a molecular mimic of at least five amino acids. Tr. 44-47; Pet. Ex. 15

[125] The undersigned acknowledges that these cases do not necessarily reflect HPV vaccine and/or optic neuritis, but generally support the Court's acceptance of molecular mimicry as a sound and reliable theory.
[126] Havla et al., *supra* note 15.
[127] Zamvil & Slavin, *supra* note 16.
[128] Rostasy et al., *supra* note 17.
[129] Sagan et al., *supra* note 18.
[130] Sellebjerg et al., *supra* note 8.
[131] Steinman, *supra* note 20.
[132] Ota et al, *supra* note 33.
[133] Pette et al., *supra* note 39.
[134] Gautam et al., *supra* note 24.
[135] Gautam et al., *supra* note 25.
[136] Gautam et al., *supra* note 26.
[137] Christensen et al., *supra* note 46.

at 12-14; Pet. Ex. 33[138]; Pet. Ex. 34[139]; Pet. Ex. 35[140]; Ex. 48.[141]; Pet. Ex. 49[142] ; Pet. Ex. 15 at 12-14.

Further, Dr. Steinman stated that epidemiologic studies have limitations and are unable to provide evidence on individual cases. He pointed out that *Baxter* showed that out of one million doses of the quadrivalent HPV vaccine given, 4 cases of optic neuritis occurred within 2-42 days, even though the study concluded there was no evidence that vaccines were associated with optic neuritis four to six weeks after immunization. Tr. 65-66; Pet. Ex. 41 at 5; Pet. Ex. 42 at 2. The authors acknowledged that even with large study groups, it is hard to rule out small adverse effects and generally impossible to prove that a vaccine is never associated with a particular outcome. Pet. Ex. 42 at 2-3. Further, epidemiologists rarely use the term "causation" rather they show that A is related to B with a high degree of probability and what that probability is. Tr. 66-67.

Dr. Steinman provided literature which confirms the presence of MOG, MBP, and PLP proteins in the myelin of the optic nerve which is involved in the development of optic neuritis, and that patients with optic neuritis have more of these proteins than control subjects. Pet. Ex. 46[143] at 1; Pet. Ex. 26.[144] Dr. Steinman submits that he has shown that these human proteins linked to the development of optic neuritis look similar to the viral proteins HPV16 L1 and HPV18 L1 contained in the Cervarix vaccine and were the substantial contributing factor in petitioner's development of optic neuritis, along with the lipid-based adjuvant in the Cervarix vaccine. Tr. 63-64.

Dr. Whitton argued that homology alone is not sufficient, there must be cross-reactivity that leads to disease. He emphasized that "molecular mimicry is real," but has not been shown to cause detectible pathology. Thus, the notion that homology alone is sufficient to trigger an immune-mediated disease must be dismissed. Resp. Ex. C at 10. Dr. Whitton has advanced the same argument for years and claimed that Dr. Steinman misuses BLAST searches and the IEDB to support his theory of molecular mimicry in vaccine cases.

Dr. Lotze also challenged Dr. Steinman's reliance on sequences of homologies, submitting that there are no in-vitro or in-vivo publications that any sequences of the L1 capsid protein from HPV16 or HPV18 can induce immune cells to activate against the central nervous system. Resp. Ex. A at 7. Dr. Lotze referenced multiple large-scale studies, including a 2018 meta-analysis of HPV and demyelinating disease, which concluded that, despite a small number of reports of demyelinating diseases including optic neuritis following HPV vaccination, the evidence supports an "incidental association between vaccination and demyelination rather than a causal relationship." Resp. Ex. A at 13.

Drs. Whitton and Lotze's arguments regarding epidemiologic studies, animal models, and identification of specific peptide structures, sequences, and molecular mimics and a showing of

[138] Gautam et al., *supra* note 24.
[139] Gautam et al., *supra* note 25.
[140] Gautam et al., *supra* note 26.
[141] Lanz et al., *supra* note 47.
[142] Robinson & Steinman, *supra* note 48.
[143] Sellebjerg et al., *supra* note 8.
[144] Havla et al., *supra* note 15.

causality to the HPV vaccine is contrary to Vaccine Program case law and places too heavy a burden on petitioner. Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). It is not petitioner's burden to prove his theory with this level of specificity. *Knudsen*, 35 F.3d at 549.

Having evaluated all the evidence presented, I find that Dr. Steinman has provide a sound and reliable medical theory demonstrating that the Cervarix vaccine can cause or trigger optic neuritis through molecular mimicry. Accordingly, I find that petitioner has satisfied her burden of proof with respect to *Althen* Prong I.[145]

2. *Althen* Prong II

Under *Althen* Prong Two, petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Capizzano*, 440 F.3d at 1324 (quoting *Althen*, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" *Pafford*, 451 F.3d at 1356 (internal citations omitted). The petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific

[145] While not fully developed, the adjuvants contained in the Cervarix vaccine, alum and AS04, which are different than those contained in the Gardasil vaccine, were discussed during the hearing. Tr. 165. After the hearing, petitioner filed additional literature which discussed AS04 which states that the AS04-adjuvanted HPV vaccine "induces a high and sustained immune response against HPV, including high levels of neutralizing antibodies at the cervical mucosa in women aged 15-55 years." Pet. Ex. 53 at 1. The mechanism of AS04 was evaluated in both human and mice cells. The data provided evidence for the molecular and cellular basis of observed immunogenicity, efficacy, and safety profile for the formulation. *Id*. Clinical study of the addition of AS04 to the HPV vaccine showed high vaccine-elicited antibody responses and the induction of high levels of memory B cells. *Id*. Contrary to Dr. Whitton's testimony that there is no cross-protection of HPV subtypes, the vaccine containing AS04 elicited cross-protection against other oncogenic HPV types, including HPV31, 33, and 45, which are not contained in the vaccine. *Id*; Tr. 107. Aluminum salts have been used as vaccine adjuvants for many years, but they are often not sufficient when higher levels of antibodies or T-cell-mediated immunity is required. Pet. Ex. 53 at 2. The introduction of AS01, AS03, and AS04 have demonstrated their ability to promote strong humoral and cellular immune response, and AS04 specifically was selected for this HPV vaccine "to secure enhanced priming of the immune system in order to afford high protection for as long as possible – potentially for an entire lifetime." *Id*. at 2, 5. Experimental work showed that the capacity of AS04 to enhance HPV antigen-specific humoral response was optimal during the first hour after injection and totally disappeared 24 hours after injection. *Id*. at 5. The article concluded that "… there is no evidence of activation of interferon-α, a cytokine that has been associated with autoimmune disease." *Id*. at 8.

Thus, while there is no evidence of an association between autoimmune diseases and AS04, the components of and the response to the Cervarix vaccine are different than other HPV vaccines including Gardasil vaccine, which does not use this adjuvant. Therefore, the studies being relied upon herein involving the safety of other HPV vaccines which use different adjuvants, particularly Gardasil, cannot necessarily be applied to the Cervarix vaccine. While this distinction is helpful to petitioner, it is not necessarily dispositive given that there is precedent for finding that Gardasil can cause CNS demyelination via molecular mimicry, even in the absence of the Cervarix adjuvant. *See White v. Sec'y of Health & Human Servs*., No. 15-1521V, 2019 WL 7563239 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (accepting that Gardasil can cause acute transverse myelitis); *B.A. v. Sec'y of Health & Human Servs*., No. 11-51V, 2018 WL 6985218 (Fed. Cl. Spec. Mstr. Dec. 6, 2018), *redacted opinion issued*, No. 11-51V, 2019 WL 460140 (Fed. Cl. Spec. Mstr. Jan. 8, 2019) (accepting that Gardasil can cause severe chronic headaches).

or medical communities to establish a logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1325. Instead, petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. *Id.* at 1325-26.

In evaluating whether this prong is satisfied, medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. *Cucuras*, 993 F.2d at 1528; *but see Kirby v. Sec'y of Health & Human Servs*., 993 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying that *Cucuras* does not stand for proposition that medical records are presumptively accurate and complete). While the medical records and opinions of treating physicians must be considered, they are not binding on the special master. The Vaccine Act specifically provides that the "diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court." § 13(b)(1)(B).

Here, I find preponderant evidence of a logical sequence of cause and effect establishing that the Cervarix vaccination administered to petitioner on March 20, 2014 caused/triggered her optic neuritis. All the experts agree that petitioner was appropriately diagnosed with optic neuritis. As detailed above, petitioner has offered a sound a reliable theory detailing the components of the Cervarix vaccine, their similarities to the MOG and PLP proteins present on the myelin of the optic nerve, and how optic neuritis can occur through molecular mimicry. None of the experts disputed the components of the Cervarix vaccine, the presence of MOG, PLP, or MBP on the myelin of the optic nerve, their involvement in the development of optic neuritis, or molecular mimicry as the mechanism by which optic neuritis could occur.

Petitioner's medical records provide circumstantial evidence in support of vaccine causation. Petitioner was a healthy 15-year-old when she received her third Cervarix vaccine on March 20, 2014. Pet. Ex. 13 at 1. On May 5, 2014, she presented to the pediatrician with a one-week history of headache. Pet. Ex. 1 at 69. She returned the following day, reporting daily frontal headache for seven to nine days that came and went but always present, with pain and pressure behind her eye and in her forehead. *Id*. at 72. She was assessed with acute sinusitis, but a neurology visit was suggested. *Id*. at 74. Two days later, petitioner presented to the ER with ten days of right-sided headache with increasing pain. Pet. Ex. 8 at 8, 13. A head CT was normal. *Id*. at 19-20. She experienced some improvement with Toradol, Reglan, Benadryl, and IV fluids, but still had pain when she moved her eye. *Id.* at 66, 69.

Petitioner was finally diagnosed with optic neuritis by her ophthalmologist Dr. Wasserman on May 21, 2014. Pet. Ex. 5 at 2. She was referred and presented to Wills Eye in Philadelphia, Pennsylvania that day. *Id*. at 1-2. She reported 33 days of headache, three weeks of pain on the right side of her head and mildly blurred vision that worsened over the past week. Her recent HPV vaccine was noted. Pet. Ex. 6 at 27-28; Pet. Ex. 7 at 29. A brain MRI showed diffuse enlargement and enhancement of the entire right optic nerve with extension to the optic chiasm compatible with optic neuritis, but no brain lesions and no intracranial mass. Pet. Ex. 7 at 156-59. She was admitted for "pulse steroids" for right optic neuritis of unclear etiology. *Id*. at 38. CSF testing showed elevated glucose but was otherwise normal. Her antineutrophil cytoplasmic antibody tests were all negative, as was ANA. *Id*. at 58. Her vision was significantly improved after three days of pulsed steroids, and she was discharged on oral steroids. Petitioner was to follow up with ophthalmology

and the Multiple Sclerosis Clinic at Jefferson in one week. *Id*. She continued to follow up at Will's Eye in the months that followed. Pet. Ex. 6 at 4, 6, 8.

Petitioner saw Dr. Leist on June 18, 2014. Pet. Ex. 3 at 4, 22-25. Her history was noted. Pet. Ex. 3 at 4, 12-17. An intake form completed at this visit by petitioner's mother listed the Cervarix vaccine as a possible "root cause" of her optic neuritis. *Id*. at 42. At her follow-up visit August 12, 2014, petitioner reported her vision was almost back to normal. *Id*. at 1. The remainder of her medical records address the sequela of her optic neuritis.

The medical records contain no evidence of viral prodrome, other neurological symptoms, tick or cat exposure,[146] or any other cause of petitioner's optic neuritis other than the HPV vaccine. Pet. Ex. 6 at 27-28; Pet. Ex. 7 at 29. Respondent did not offer another cause other than to say that a percentage of optic neuritis is idiopathic. The Federal Circuit has rejected statistical likelihood alone as proof of causation. *Boatmon*, 941 F.3d at 1363 (citing *Knudsen*, 35 F.3d at 550 (rejecting alternative cause theory based on "[t]he bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies")). Further, petitioner's immediate response to steroids strongly suggests that her isolated optic neuritis event was an autoimmune response.

Here, a logical sequence of cause and effect consistent with vaccine causation exists and petitioner need not eliminate other potential alternative causes particularly where none exist. *See Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1149-52 (Fed. Cir. 2007) (finding petitioner does not bear the burden of eliminating alternative independent potential causes).

Accordingly, the undersigned finds that petitioner has proven by preponderant evidence a logical sequence of cause and effect establishing that her optic neuritis was caused and/or triggered by the Cervarix vaccine and has therefore satisfied the second *Althen* prong.

3. *Althen* Prong III

Althen Prong III requires petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That phrase has been defined as a "medically acceptable temporal relationship." *Id*. The petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under *Althen* Prong One). *Id.*; *Koehn v. Sec'y of Health & Human Servs.*, 773 F.3d 1239, 1243 (Fed. Cir. 2014); *Shapiro v. Sec'y of Health & Human 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).

Respondent's experts do not directly address timing in this case, other than Dr. Lotze's reference to the package insert for Cervarix vaccine which contains headache within 7-30 days after vaccination, and his statement that petitioner's headache began 38 days later after her receipt

[146] *See* Pet. Ex. 6 at 27-28; Pet. Ex. 7 at 29.

of the vaccination and therefore was not associated with the vaccine. Resp. Ex. A at 4. While a headache may be a symptom of optic neuritis, the package insert discusses headache alone and not the onset of optic neuritis, and neither did Dr. Lotze.

A timeframe of three to 42 days has been accepted in cases involving peripheral and central nervous system diseases and injuries. Further, this time frame has been acknowledged as appropriate in other Vaccine Program cases in which molecular mimicry has been offered as the causal mechanism. *See, e.g.*, *Koller*, 2021 WL 5027947, at *23; *Barone*, 2014 WL 6834557, at *13 ("[S]pecial masters have never gone beyond a two-month (meaning eight week) interval in holding that a vaccination caused a demyelinating illness."). Petitioner's onset of symptoms associated with optic neuritis began within this 3-to-42-day period.

Therefore, the undersigned finds that petitioner has met her burden of proof as to *Althen* Prong III.

B. Alternative Causation

Because the undersigned concludes that petitioner has established a prima facie case, petitioner is entitled to compensation unless respondent can put forth preponderant evidence "that [petitioner's] injury was in fact caused by factors unrelated to the vaccine." *Whitecotton v. Sec'y of Health & Human. Servs.*, 17 F.3d 374, 376 (Fed. Cir. 1994), *rev'd on other grounds sub nom.*, *Shalala v. Whitecotton*, 514 U.S. 268 (1995); *see also Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007). As discussed above in the analysis of *Althen* Prong II, the respondent did not offer an alternative diagnosis or provide any evidence to show that petitioner's optic neuritis was caused by anything other than vaccination and relied only on statistics that one third of optic neuritis cases are idiopathic, which is not permissible. *See Boatmon*, 941 F.3d at 1363. Thus, respondent did not offer or prove by a preponderance of evidence that petitioner's injury was "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

VI. Conclusion

Based on the record as a whole and for the reasons discussed above, the undersigned finds there is preponderant evidence to satisfy all three *Althen* prongs and to establish that petitioner's Cervarix vaccination caused and/or triggered her optic neuritis. The undersigned therefore finds that petitioner is entitled to compensation. Accordingly, this matter shall proceed to damages.

IT IS SO ORDERED.

s/Mindy Michaels Roth
Mindy Michaels Roth
Special Master