In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-362V
(to be published)

BRYAN MACIEL, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Corcoran Filed: October 12, 2018 Decision; Denial of Entitlement; Multiple Sclerosis ("MS"); Human Papillomavirus Vaccine ("HPV"); Significant Aggravation.

Clifford J. Shoemaker, Shoemaker, Gentry & Knickelbein, Vienna, Va., for Petitioner.

Debra Filteau Begley, U.S. Dep't of Justice, Washington, D.C., for Respondent.

DECISION DENYING ENTITLEMENT[1]

On April 10, 2015, Elias and Kelly Maciel filed a Petition under the National Vaccine Injury Compensation Program (the "Vaccine Program"[2]) on behalf of Bryan Maciel (then a minor)[3] alleging that he developed multiple sclerosis ("MS") and optic neuritis as a result of receiving doses of the human papillomavirus ("HPV") vaccine on August 28, 2013, October 13,

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

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. § 300aa-10 through 34 (2012)) (hereinafter "Vaccine Act" or "the Act"). All subsequent references to sections of the Vaccine Act shall be to the pertinent subparagraph of 42 U.S.C. § 300aa.

[3] The caption was updated after Bryan Maciel became eighteen, rendering him the proper party in interest.

2013, and March 6, 2014, and/or that the last dose of HPV vaccine significantly aggravated his underlying MS. Petition ("Pet.") (ECF No. 1) at 1.

A hearing in this matter was held on March 22, 2018. After consideration of the record and testimony provided at hearing, I find that Petitioner is not entitled to a compensation award. The parties' experts agree that Petitioner's MS began (both in a clinical and radiologic sense) *before* he received his final dose of the HPV vaccine – leaving only significant aggravation as a potential claim (since the record does not otherwise support the conclusion that any of the earlier HPV doses were causal of his MS). But Petitioner has not established a plausible causation theory that the HPV vaccine *could cause* an MS relapse/exacerbation, and he has not offered sufficient preponderant evidence that in this specific case the final HPV vaccine he received *was* the cause of any subsequent symptoms he experienced, or that it worsened his MS's overall course.

I. Factual Background

The record in this case consists of Mr. Maciel's medical records, affidavits from fact witnesses, the reports and testimony of two experts, and medical or scientific literature submitted by the parties in support of their respective positions. I have reviewed the entire record as required by the Vaccine Act.

HPV Vaccinations and Pre-Vaccination History

On August 28, 2013, Petitioner received the first dose of the HPV vaccine at All Better Pediatric Group in Coconut Creek, Florida, when he was fourteen. Ex. 15 at 4-5; Ex. 7 at 45. Two subsequent doses were administered on October 30, 2013, and March 6, 2014, respectively. Ex. 15 at 2-3; Ex. 7 at 42-44. No adverse reactions were noted at any of the times Petitioner received the vaccinations. Mr. Maciel was fourteen years old when he received the last HPV dose in March 2014. Ex. 7 at 43.

Prior to receiving the first HPV dose, Petitioner was relatively healthy. Earlier records indicate treatment for common ailments. *See, e.g.*, Ex. 9 at 6 (August 17, 2010 treatment for ear pain and swelling), 7 (June 6, 2011 treatment for cough), 10 (December 6, 2012 sprained thumb), 11 (September 21, 2011 intermittent pain in lower back and hip), 19 (September 7, 2010 treatment for ear pain), 22-24 (August 23, 2010 treatment for tympanometry and cerumen removal). It does not appear that Petitioner had any history of neurologic symptoms in the time period before completion of the HPV vaccine series (other than those discussed below). The March 6, 2014 record establishing Petitioner's receipt of the third HPV vaccine dose says nothing about any symptoms he may have been experiencing at that time, and no complaints were voiced to his treaters. Ex. 7 at 42-43.

MS and Optic Neuritis Symptoms Around Time of Third HPV Dose

On March 8, 2014 (two days following the receipt of the third dose of HPV), Petitioner presented to the West Boca Medical Center emergency room in Boca Raton, Florida, for blurred vision, and a headache. Ex. 14 at 107, 114, 118.[4] Petitioner reported an onset of one week prior, and suggested that his symptoms were variable. *Id.* at 114 ("patient has intermittent left blurred vision, sometimes related with headache . . . since the last week"), 135 ("decreased vision intermittent x one week OS"). At the time of this ER visit, Mr. Maciel did not report pain (and was able to play basketball and attend school the day before) – but at the same time indicated that he felt his symptoms were "getting progressively worse" overall. *Id.* at 114, 118, 119.

Petitioner was evaluated by Dr. Luis Rios during the visit. Upon examination, Dr. Rios noted diminished acuity in Mr. Maciel's left eye, but no recent infection. Ex. 14 at 114. A CT scan conducted during the visit was normal, and no acute intracranial abnormalities were noted. *Id.* at 135-36. Following an ophthalmologic exam, Petitioner was diagnosed with an ocular migraine. *Id.* at 122. He was prescribed Ibuprofen, discharged, and directed to follow-up the next day if his symptoms did not improve. *Id.* at 112.

Petitioner returned to the emergency room the next day, on March 9, 2014, complaining of persistent blurred vision in the left eye and accompanying headaches. Ex. 14 at 62, 63-65. Upon admission, he again informed treaters that onset of his symptoms began one week prior to presentation. *Id.* at 68 ("patient states: left eye intermittent blurred vision x1 week with left-sided headaches"). A repeat eye exam revealed decreased visual acuity of 20/200 in the left eye. *Id.* at 64. An MRI (with and without contrast[5]) was ordered and revealed multiple white matter lesions in the cerebral hemisphere and left cerebellar peduncle, as well as a suspected lesion on the anterior left optic nerve. *Id.* at 98. The larger legions showed "very faint gadolinium enhancement" and a possible "faint area of enhancement" in the anterior left optic nerve. *Id.* Petitioner's treating neurologist suspected MS and recommended that Mr. Maciel be transferred to Miami Children's Hospital ("Miami Children's") for further treatment. *Id.* Blood work completed in the emergency

[4] A history obtained in connection with Petitioner's subsequent Jackson Health System hospitalization beginning March 15, 2014 (discussed below), suggests that Mr. Maciel had an additional ER visit on March 7, 2018 – the day after vaccination. *See* Ex. 10 at 19. I am unable to locate in the filed materials a record corroborating this ER visit; however, this reference is otherwise consistent with the overall facts of the case (i.e., that Petitioner experienced additional headaches and blurred vision beginning at least a day after vaccination, and that eventually he was admitted to Miami Children's).

[5] Lesion enhancement on MRI occurs after the uptake in the lesion of a gadolinium-based contrast agent injected into a subject's blood. *See W.C. v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 440, 444 (2011); *see also* Tr. at 94-95 (Dr. Javed's explanation of use of enhancement in conducting MRIs). The uptake reveals an ongoing/existing breakdown of the blood-brain barrier (since the contrast agent is able to go into the brain), and in turn suggests an enhanced lesion is more recent in nature. *See W.C.*, 100 Fed. Cl. at 444. Such a breakdown can trigger neurological injury, by allowing infectious or inflammatory agents into the brain and central nervous system, causing damage. *Id.*

room was notable for an elevated eosinophil[6] percentage (seven percent), although the erythrocyte sedimentation rate ("ESR")[7] and C-reactive protein ("CRP")[8] levels were both within the normal range. *Id.* at 100-02.

Petitioner arrived at Miami Children's that same day. Once again, Mr. Maciel reported that his symptoms (including blurred vision and headaches) had begun six days earlier and resolved, but then returned on March 7, 2018 (the day after receiving the final HPV dose). Ex. 13 at 501-02. No fever or other associated symptoms were noted. *Id.* at 502. The current headache he was experiencing was characterized as moderate and responsive to Ibuprophen. *Id.* But the new headache was not deemed by Petitioner to be distinct in severity from the prior, resolved headache, although his vision was getting blurrier. *Id.* at 501-02 ("[h]e was pain free for 3 days and then 2 days ago he started with the *same* left-sided headache and worsening blurry vision"). A record obtained the next day, March 10, 2014, by Dr. Ann Hyslop again noted that Petitioner's symptoms had progressed from their onset March 3rd and that they were all part of the same progressive course. *See id.* at 114 ("[s]ymptoms began on 3/3/14 intermittently and became progressively worse over the week").

A repeat MRI performed after Petitioner's arrival at Miami Children's revealed "diffuse bilateral hemispheric areas of signal abnormality" in the white matter, along with "signal abnormality and abnormal enhancement" in the left optic nerve. Ex. 13 at 153. A lumbar puncture and subsequent cerebrospinal fluid ("CSF") analysis revealed "all evoked" oligoclonal bands, which treaters deemed consistent with an MS diagnosis. *Id.* at 11, 129-31; Ex. 7 at 10. Both a lupus panel and an infectious disease panel were negative. Ex. 13 at 11. Petitioner also tested negative for neuromyelitis optica ("NMO") antibodies. *Id.* at 130. Mr. Maciel was treated with three days of Solu-Medrol, and later transitioned to oral steroids. *Id.* at 11. His headaches seemed to resolve quickly, although the blurred vision continued. *Id.* at 79. Upon discharge on March 13, 2014, it was noted that Mr. Maciel's test results supported a diagnosis of MS along with retrobulbar optic neuritis in the left eye. *Id.* at 11-12, 107. He was directed to follow-up with his ophthalmologist

[6] An eosinophil is a granular leukocyte (or disease-fighting white blood cell) with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, rounding granules that are uniform in size. *Dorland's Illustrated Medical Dictionary* 629 (32nd ed. 2012) (hereinafter *Dorland's*). A higher than normal level of eosinophils most often indicates a parasitic infection, an allergic reaction, or cancer. *See Eosinophilia*, Mayo Clinic, https://www mayoclinic.org/symptoms/eosinophilia/basics/definition/sym-20050752 (last accessed on Oct. 4, 2018).

[7] ESR is a blood test used to show inflammatory activity in the body. *Sed Rate (Erythrocyte Sedimentation Rate)*, Mayo Clinic, https://www mayoclinic.org/tests-procedures/sed-rate/about/pac-20384797 (last accessed Sept. 12, 2018). It measures the distance red blood cells fall in a test tube in one hour. *Id.* The further the cells descend in the tube, the greater evidence of an existing inflammatory response of the immune system. *Id.*

[8] CRP is also a test used to measure inflammation in the body. *C-Reactive Protein Test*, Mayo Clinic, https://www.mayoclinic.org/tests-procedures/c-reactive-protein-test/about/pac-20385228 (last accessed Sept. 13, 2018). It measures the amount of C-reactive protein in the blood via a simple blood test. *Id.* The results can indicate a patient's risk for infection or heart disease, for example. *Id.*

and neurologist for further evaluation, and prescribed Prednisone and Zantac for maintenance of his condition. *Id.* at 12, 109.

On March 14, 2014, Petitioner presented to Dr. Roberto Lopez-Alberola, a physician with the neurology department at the University of Miami Miller School of Medicine, for further treatment related to his hospitalization. Petitioner again reported a history of blurred vision in the left eye and headaches beginning two weeks prior to the visit. Ex. 5 at 10 ("onset dates back to 2 weeks"). Upon examination, Mr. Maciel was reportedly improving, but still experiencing left eye blurriness. *Id.* at 11. After reviewing Petitioner's health history, Dr. Lopez-Alberola concluded that the differential diagnosis was NMO versus MS (pending completion of Mr. Maciel's work up). *Id.* He recommended that Petitioner continue to follow-up for MRI monitoring, and prescribed Naproxen for headaches. *Id.*

The next day, on March 15, 2014, Petitioner was admitted to the emergency room at Jackson Health Systems in Miami, with complaints of worsening symptoms. Ex. 10 at 15-16. During this visit, Petitioner reported additional symptoms (including stomach pain, nausea, vomiting, and numbness and tingling in his left leg). *Id.* at 23. Following admittance, Mr. Maciel was treated with IV steroids and Nexium for gastrointestinal symptoms. *Id.* at 24. He was evaluated by a neuro-ophthalmologist, Dr. Sean Gratton, who (consistent with earlier treaters) opined that Petitioner likely had MS with accompanying optic neuritis. *Id.* at 28. Petitioner again tested negative for NMO antibodies. *Id.* at 29-30. A repeat MRI otherwise revealed a number of non-enhancing lesions, which was noted to be consistent with an ongoing/preexisting demyelinating process suggestive of MS. *Id.* at 34; Ex. 8 at 53-55. It also revealed a possible arachnoid cyst. Ex. 10 at 34. Petitioner was discharged three days later on March 18, 2018, and directed to follow-up with his treating neurologist. *Id.* at 18.

Petitioner presented for a repeat MRI on March 20, 2014, to evaluate his optic nerves. Ex. 8 at 58. No intraorbital mass lesions were identified, and no abnormal enhancement or edemas along the bilateral optic nerve were noted. *Id.* A thoracic MRI conducted on March 21, 2014, revealed spinal fluid collection between T1 and T2 signals that were thought to be consistent with an arachnoid cyst. *Id.* at 56; Ex. 10 at 39-40. An additional brain MRI conducted on March 28, 2015 continued to reveal the presence of lesions along with oligoclonal banding (but showed no new enhancement). Thereafter, Petitioner presented to Dr. Lopez-Alberola for a neurology follow-up on March 28, 2014. Ex. 5 at 8-9. Treatment notes indicated that Mr. Maciel had experienced no new symptoms since his discharge from Jackson Health Systems. *Id.* at 8. Based on the recent MRI evidence, Dr. Lopez-Alberola continued to suspect that Petitioner had MS and prescribed Avonex. *Id.* at 9.

Subsequent Treatment for MS

On March 31, 2014, Petitioner presented to Dr. Byron Lam, a neuro-ophthalmologist, for monitoring. Ex. 8 at 30-33. During this visit, Mr. Maciel reported the same history (loss of visual acuity and headaches beginning on March 3, 2014). *Id.* at 30 ("optic neuritis OS → 3/3/14"). Treatment notes also indicate that Petitioner had been diagnosed with MS "two weeks ago." *Id.* An examination revealed that Mr. Maciel continued to experience decreased visual acuity in the left eye. *Id.* at 31. Dr. Lam assessed Mr. Maciel and concluded his symptoms were consistent with an onset of optic neuritis. *Id.* at 33. He noted that Petitioner had started Avonex to treat his MS, and recommended a follow-up appointment in three months. *Id.*

On May 10, 2014, Petitioner was admitted to the hospital for a third time for treatment of an MS flare that caused blurred vision in the left eye and tingling in his hands and feet. Ex. 10 at 45-46. The attending physician, Dr. Luis Garcia-Chacon, noted that Petitioner had been diagnosed with MS in March 2014. *Id.* at 48. An MRI conducted on May 8, 2014, showed stable, non-enhancing lesions, and internal improvement in the signal changes seen in the left optic nerve, but some persistent signal abnormality. Ex. 5 at 5. Repeat cervical and thoracic MRIs were also conducted. The cervical MRI was unremarkable, but the thoracic MRI continued to show fluid collection at the T1-T2 level (consistent with an arachnoid cyst). *Id.* at 6-7. Following additional rounds of Solu-Medrol steroid therapy, Petitioner was discharged on May 15, 2014, with a diagnosis of an MS flare with noted clinical improvement. *Id.* at 45-47. The discharging physician directed Mr. Maciel to follow-up with his treating neurologist and ophthalmologist for further evaluation. *Id.* at 47.

After his third hospitalization, Petitioner continued to see treaters tasked with monitoring his condition. On July 30, 2014, Mr. Maciel presented to Dr. Lopez-Alberola, who noted the recent flare of optic neuritis in May 2014. Ex. 5 at 3-7. Upon examination, Dr. Lopez-Alberola assessed Petitioner with continued left eye blurriness and intermittent numbness and tingling in the feet and ankles, although it was also noted that no vision worsening was reported at this time. *Id.* at 3. Dr. Lopez-Alberola increased Petitioner's Avonex dosage. *Id.* at 7. Based on the radiologic evidence as of May 8, 2014, and Mr. Maciel's symptom course to date, Dr. Lopez-Alberola's diagnosis remained "2 episodes of optic neuritis left eye, with diagnosis of [MS]." *Id.*[9] He scheduled follow-up MRIs for September 2014, and recommended a follow-up appointment in four months. *Id.*

A few months later, on September 18, 2014, Mrs. Maciel discussed with Petitioner's primary care physician, Dr. Renato Berger, her concern that her son's HPV vaccinations could be related to his MS (in what appears to be the first record reference to the HPV vaccine as possibly having a connection to Petitioner's MS diagnosis). Ex. 7 at 34 ("as per mom[,] hpv gave him seizures and multiple sclerosis"). In particular, she expressed concern regarding "aluminum and

[9] Dr. Lopez-Alberola is referencing one episode in March 2014 and one in May 2014. *See* Ex. 5 at 7-8.

other heavy metals" present in the vaccine, and discussed obtaining bloodwork "to prove it." *Id.* Office notes indicate that Dr. Berger counseled Petitioner's mother for roughly an hour, and assured her that the HPV vaccine did not contain the above-referenced "heavy metals." *Id.* Despite, Mrs. Maciel's assertions, treatment notes do not suggest that Dr. Berger offered any opinion concerning vaccine causation.

On November 11, 2014, Mr. Maciel returned to see Dr. Lam for a follow-up appointment related to his optic neuritis course. Treatment notes indicated that Petitioner had been improving since his May 2014 flare, but still had decreased vision in his left eye. Ex. 8 at 8. No additional flares of symptoms were noted at this time.

The remainder of Petitioner's records pertain to treatment for various ailments and well-adolescent visits that appear unrelated to receipt of the HPV vaccinations or his treatment for MS/optic neuritis. *See, e.g.*, Ex. 7 at 35-36 (August 29, 2014 well-adolescent visit with no noted concerns apart from history of MS diagnosis and optic neuritis), 37-38 (June 3, 2014 and May 22, 2014 pink eye treatment), 39-40 (May 20, 2014 acute conjunctivitis and acne treatment), and 41 (April 16, 2014 referral for depression).

II. Fact Witness Affidavits

In addition to the medical records discussed above, Petitioner offered two affidavits, one from Elias Maciel and one from Kelly Maciel (his father and mother). The affidavits are dated April 8, 2015, and April 7, 2015, respectively. *See* ECF No. 1 at 3-4 ("Maciel First Aff."), 5-6 ("Maciel Second Aff.").

The Maciels' affidavits detail their recollection of Mr. Maciel's symptoms following his receipt of three doses of the HPV vaccine, and are generally consistent with the medical record discussed above. Apart from confirming that Mr. Maciel began experiencing symptoms (including headaches and blurry vision) "within hours" of receiving his third dose of HPV on March 6, 2014, the Maciels also acknowledged that Petitioner experienced adverse symptoms *prior* to March 6th (though they did not give an exact date). Maciel First Aff. at 3; Maciel Second Aff. at 5. In their view, however, Petitioner's symptoms prior to March 6th (limited to intermittent headaches) were attributable to the second dose of HPV he received on October 30, 2013. Maciel First Aff. at 3. Even so, despite their statements, the Maciels acknowledged they did not seek medical treatment for Petitioner's symptoms until his emergency room presentation following his third dose of HPV in March 2014. *Id.*

Apart from the above, the affidavits briefly discuss Petitioner's condition as of April 2015. At that time, the Maciels noted that Petitioner continued to seek treatment from his neurologist and ophthalmologist, and received weekly injections of Avonex (causing him to experience

fatigue, body aches, and fever). Maciel First Aff. at 3. The affidavits do not otherwise discuss Petitioner's current condition and no updated affidavits have been filed to date.

III. Expert Opinions

A. *Dr. Carlo Tornatore*

Dr. Tornatore authored two reports and testified at the entitlement hearing on Petitioner's behalf. *See* Expert Report, dated May 5, 2016 (ECF No. 17-2) ("First Tornatore Rep."); Expert Report, dated Jan. 13, 2017 (ECF No. 23-2) ("Second Tornatore Rep."). Dr. Tornatore opined that Mr. Maciel suffered from pre-existing MS (presenting as optic neuritis) that was significantly aggravated by his receipt of the third dose of the HPV vaccine. Tr. at 18, 48.

Dr. Tornatore is a board-certified neurologist. *See* Exhibit 28, dated Mar. 21, 2018 (ECF No. 39-2) ("Tornatore CV"). He graduated from Cornell University with a Bachelor of Arts in Neurobiology, and attended Georgetown University Medical Center, where he received a Master of Science in Physiology. *Id.* at 2; Tr. at 5. He subsequently graduated from medical school at Georgetown University School of Medicine, completing a residency in the Department of Neurology at Georgetown University Hospital. Tornatore CV at 2. He also completed a fellowship in molecular virology at the National Institute of Health in Bethesda, Maryland. *Id.* Dr. Tornatore has published multiple articles addressing cell biology and pathology of demyelinating disorders. *Id.* at 7-14. Currently, he serves as Vice Chairman in the Department of Neurology at MedStar Georgetown University Hospital, and as a Professor of Neurology at Georgetown University Medical Center. Tornatore CV at 3; Tr. at 5. Dr. Tornatore represented that he is an immunologist as well – although, this is not his specialty, and his CV does not reflect a practice-oriented, ongoing focus on the subject. Tr. at 6-7.

At hearing, Dr. Tornatore began his testimony by briefly describing MS and its common clinical symptoms. Dr. Tornatore characterized MS as an autoimmune demyelinating disease of the central nervous system ("CNS") with identifiable chronic inflammatory and neurodegenerative components. Tr. at 8; First Tornatore Rep. at 8. Although the immune system initiates a chronic inflammatory process in the CNS in patients with MS, the initial antigenic stimulus that triggers the autoimmune reaction is unknown. Tr. at 8; First Tornatore Rep. at 8. According to Dr. Tornatore, however, it is believed that foreign antigens entering the body (e.g., a viral or bacterial infection, or vaccination) activate the immune system, and (in rare circumstances), the activation becomes "misdirected" and the immune system "attack[s] components of the nervous system." First Tornatore Rep. at 8.

A typical course of MS can include paralysis, sensory disturbances, incoordination, and visual impairment. Tr. at 10; *see* L. Steinman, et al., *Multiple Sclerosis: Deeper Understanding of Its Pathogenesis Reveals New Targets for Therapy*, 25 Ann. Rev. Neurosci. 491, 491 (2002), filed

as Ex. 22 (ECF No. 16-6) ("Steinman"). MS often begins with an attack lasting for days to weeks, followed by remission lasting months to years. *Id.* at 491-92. Dr. Tornatore further defined the various forms of MS as primary progressive (no specific attacks but evidence of worsening of overall condition and accompanying lesions), relapsing/remitting, and secondary progressive (which can involve relapsing/remitting, primary progression, or both). Tr. at 10-11. The course of MS, while progressive, is highly variably from patient to patient, and treatment focuses on management of symptoms in order to minimize the severity of the disease's course. *Id.* at 9. Dr. Tornatore noted that MS is primarily a female-predominant disease (75 percent), which in his view rendered Mr. Maciel's case as "a little unusual" given his gender. *Id.* at 11.

Upon review of the medical record, Dr. Tornatore opined that Mr. Maciel's presenting MS symptoms (which he characterized as "mild optic neuritis") began prior to his receipt of the third dose of HPV. Tr. at 7-8, 11 ("his first symptoms were that first week of March, . . . when he started to have vision blurriness and pain"), 48, 75-76. Dr. Tornatore identified record evidence of MS-related symptoms prior to the vaccination that he deemed significant in light of Petitioner's claim (including MRI evidence, CSF findings, and the March 8, 2014 clinical presentation). Tr. at 12 ("Mr. Maciel clearly had . . . some evidence of demyelination on his scans prior to coming to medical attention the beginning of March"), 47-48 ("we looked at his MRI and we looked at his CSF . . . I think all of us would agree that this is MS"). Although he could not pinpoint the exact date Petitioner's MS started, Dr. Tornatore concluded (based on the medical record evidence) that his neurologic symptoms (including blurred vision and accompanying headaches) clearly existed by March 3, 2014 (three days prior to receiving the third dose of the HPV vaccine). *Id.* at 13 (citing Ex. 14 at 114-15; Ex. 13 at 4, 5-8), 48. He opined that Petitioner's initial presenting symptoms were best classified as an MS "relapse." *Id.* at 75. However, he characterized the post-vaccination symptoms as more severe than what Mr. Maciel experienced before March 6th. *Id.* at 19-20.

In Dr. Tornatore's view, the alleged vaccine-induced injury in this case is best understood as a significant aggravation of preexisting MS, attributable to the HPV vaccine being administered in the midst of an MS attack. Tr. at 15-16.[10] Based on Petitioner's medical records, Dr. Tornatore concluded that Mr. Maciel's March 3rd optic neuritis symptoms resolved prior to his receipt of the third dose of the HPV vaccine, but subsequently returned post-vaccination (thus, evidencing an immediate "worsening" following vaccine administration). *Id.* at 42. Petitioner seemed healthy at the time of vaccination, but clearly was not thereafter. *Id.* at 66-67. Despite "resolving," however, Dr. Tornatore explained that Petitioner likely had some "baseline inflammation" that could remain

[10] Dr. Tornatore declined to extend the concept of challenge/rechallenge to the present matter (which would implicate Petitioner's two previous doses of the HPV vaccine). Tr. at 77. Challenge-rechallenge is "a paradigm for exploring whether one substance caused an adverse reaction. Under this model, an individual who has had an adverse reaction to the initial vaccine dose (the challenge event) suffers a worsening of symptoms after a second or third injection (the rechallenge event.)" *Viscontini v. Sec'y of Health & Human Servs.*, No. 98–619V, 2011 WL 5842577, at *22 (Fed. Cl. Spec. Mstr. Oct. 21, 2011) (quoting *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 603 (2010) (quotations omitted)), *mot. for review den'd*, 103 Fed. Cl. 600 (2012).

in asymptomatic form. *Id.* at 42, 48.

For support, Dr. Tornatore relied on the sudden aggravation of Petitioner's symptoms post-vaccination as evidence of underlying inflammation – although he admitted that his assertion was speculative, and that he could not offer literature supporting the contention that the HPV vaccine *could cause* such an MS relapse. Tr. at 42. Nevertheless, Dr. Tornatore concluded that "but for" Petitioner receiving the third dose of HPV on March 3, 2014, Mr. Maciel would have remained symptom-free (and thus any underlying inflammation left in the wake of the resolved optic neuritis symptoms would have resolved on its own in four to six weeks). *Id.* at 31, 43. He later acknowledged, however, that it was possible Petitioner (or any MS patient for that matter) could experience future attacks at *any time* (and not caused only by vaccine receipt). *Id.* at 25.

To bulwark his argument that there was a distinction between Mr. Maciel's pre and post-vaccination symptoms, Dr. Tornatore discussed how optic neuritis (an acute disease typically characterized by a prolonged course of recovery) could reach nadir but then quickly resolve within two days (a point specifically disputed by Respondent). Tr. at 39-46. At hearing, Dr. Tornatore acknowledged that Mr. Maciel's "fluctuat[ing]" symptoms were "inconsistent" with a typical optic neuritis course. *Id.* at 16 (the disease "typically progresses to its nadir over a period of hours to days" and "[i]t doesn't come and go, come and go"), 17 ("with optic neuritis, once you start getting inflammation, it happens, and then it will resolve, but it's not going to come and go with the same episode"). He also agreed that optic neuritis is typically more severe in its pediatric form[11], but disputed that the inflammation resulting from optic neuritis would *always* be severe, arguing that within the spectrum of outcomes a mild (or even subclinical) course was plausible. *Id.* at 36, 39-40, 41, 44-45. Dr. Tornatore further acknowledged that recovery from optic neuritis usually takes two to four weeks after initial presentation – far longer than what he alleged had occurred for Mr. Maciel – but maintained that a recovery within a more "compressed" timeframe – days or even hours – was conceivable. *Id.* at 38-39, 41, 44-46.[12] He therefore proposed that absent receipt of the third HPV vaccine dose, Mr. Maciel's presenting symptoms probably would have resolved by the time of his vaccination on March 6th. *Id.* at 43. Despite such assertions, he acknowledged that he had submitted no scientific evidence supporting his contentions about a shorter course for optic neuritis. *Id.* 45.

With regard to the proposed scientific mechanism at play, Dr. Tornatore opined that the third dose of the HPV vaccine triggered in Petitioner a systematic "aberrant immune response" in the midst of an ongoing inflammatory process (in this case, an MS relapse). Tr. at 26, 58-59. As a

[11] Dr. Tornatore disputed somewhat whether this form of optic neuritis had been experienced by Mr. Maciel, given that he was a teenager at the time of the third HPV vaccine's administration. Tr. at 33-34.

[12] In defending the reasonableness of a short or mild course for optic neuritis, Dr. Tornatore pointed out that the MRI evidence suggested that Mr. Maciel's lesions (the precursors to his neuritis) had been subclinical for some period of time before his symptoms in early March – thus corroborating the fact that the clinical symptoms could also be on the mild end of the scale. Tr. at 17, 72.

general matter, he noted that vaccines work by causing inflammation. *Id.* at 22. According to Dr. Tornatore, "a diffuse response to a vaccine" by the immune system in the midst of a resolving relapse would be enough to trigger an adverse reaction. *Id.* at 55.[13] MS patients, Dr. Tornatore opined, are more susceptible to adverse vaccine reactions due to the ongoing activation of T and B cells[14] in the body occurring in the context of an existing MS flare. Tr. at 23. The augmented inflammation, he explained, occurs when T and B cells already active in response to an MS flare *secondarily* respond to the vaccine. *Id.* at 23-24. In Mr. Maciel's case, Dr. Tornatore opined, the HPV vaccine "augmented" underlying (and ongoing) inflammation already present, creating a more robust, systemic inflammatory response. *Id.* at 59-60.

In support of this component of his opinion, Dr. Tornatore filed no scientific literature directly linking the HPV vaccine to MS exacerbation.[15] Rather, he relied on case reports discussing MS exacerbation in the context of a different vaccine or a different injury (in particular, NMO).[16] *See, e.g.*, T. Menge, et al., *Neuromyelitis Optica Following Human Papillomavirus Vaccination*, 79 Neurology 285, 285-86 (2012), filed as Ex. 24 (ECF No. 16-8) (case report study detailing the development of NMO post-HPV vaccination in four patients, but concluding that the data obtained could not establish a pathogenic link); R. Owen, et al., *Immunologic Mechanisms in Multiple Sclerosis: Exacerbation by Type A Hepatitis and Skin Test Antigens*, 244 JAMA 2307 (1980), filed as Ex. 25 (ECF No. 20-2) ("Owen") (case report study of one patient who developed MS exacerbation subsequent to Hep A infection and after receipt of antigens via skin test). Dr. Tornatore also filed an article that more broadly questioned the propriety of administering vaccines (with emphasis on influenza/Hep B) to MS patients given the immune system stimulation that inevitably occurs after vaccination. *See* D. Jeffery, *The Use of Vaccinations in Patients With Multiple Sclerosis*, 19 Infect. Med. 1, 1, 4-7 (2002), filed as Ex. 19 (ECF No. 16-3) ("Jeffery"). Jeffery, however, does not mention the HPV vaccine, and further admits that most control trial

[13] At hearing, Dr. Tornatore acknowledged he is not relying on the mechanism of molecular mimicry as part of his causation opinion. Tr. at 54-55. Rather, he referenced the theory only in context of NMO to show how a vaccine "can cause" certain neurological demyelinating conditions via an autoimmune process. *Id.* at 54. Respondent, on cross, stressed that Dr. Tornatore's first report seemed to endorse molecular mimicry as a possible mechanism (for both initiating as well as exacerbating MS). *Id.* a 59; *see* First Tornatore Rep. at 8. However, at hearing, Dr. Tornatore maintained that his opinion was limited to arguing that the HPV vaccine significantly exacerbated Mr. Maciel's MS – and that this could occur without antigens from the vaccine triggering autoimmune cross-reactivity. *Id.* at 54, 59.

[14] T and B cells are the body's immunologically competent cells—T cells are responsible for cellular immunity, while B cells control humoral (blood) immunity. *Dorland's* at 1084. Both are involved in the adaptive immune response to pathogens rather than the immediate, innate immune response. *Id.*

[15] In acknowledging the absence of such literature, Dr. Tornatore nevertheless maintained that certain kinds of proof that might theoretically support his opinion - such as epidemiologic data (in the context of an MS relapse) - could never be obtained given the ethical issues involved. Tr. at 30-31.

[16] Dr. Tornatore specifically acknowledged, however, that Mr. Maciel did not suffer from NMO, which is distinguishable from optic neuritis. Tr. at 53.

studies have found no increase in MS-related disease activity following vaccination. Jeffery at 1.[17]

At hearing, Dr. Tornatore also proposed that adjuvants in the HPV vaccine could alone cause an enhanced, but aberrant, immune response within hours following administration. Tr. at 28-29. Adjuvants, he explained, are designed to create memory cells and boost a vaccine's immune response. *Id.* In the context of an MS flare specifically, Dr. Tornatore referenced experimental allergic encephalomyelitis ("EAE") vaccination models which he contended supported his theory. *Id.* at 27. EAE models involve injecting animals (usually mice) with myelin basic protein and are used to measure brain inflammation in connection with CNS demyelinating conditions (such as MS). *Id.*; *see also* Steinman at 500-01.

Dr. Tornatore next discussed the evidence in Mr. Maciel's medical records that he maintained revealed the chronic activation of the immune system. Dr. Tornatore placed great emphasis on Petitioner's lab result revealing increased levels of eosinophils. Tr. at 23, 55, 77-78. Dr. Tornatore defined eosinophilia as "an increase in the percentage or number of eosinophils in the bloodstream." *Id.* at 49. Although not a classic hallmark of an MS attack, eosinophilia is (in Dr. Tornatore's view) representative of an "allergic reaction" to some underlying stimulus or a parasitic infection (analogous to a vaccine), and a high count was in his view good evidence that an abnormal reaction to the third HPV dose had occurred (in part precisely because eosinophilia was not otherwise associated with MS). *Id.* at 23-24, 49, 77-78. Upon review of Petitioner's bloodwork, Dr. Tornatore concluded that Mr. Maciel developed eosinophilia based on a white blood cell count of seven percent eosinophils (normal reference range 0-4 percent). *Id.* at 23-24, 49. The "absolute count" of eosinophils, by contrast, was deemed by Dr. Tornatore to be less meaningful than the percentage sums of eosinophils in ascertaining abnormality. *Id.* at 49. In placing greater weight on the eosinophil percentage levels, Dr. Tornatore disputed the importance of more traditional inflammatory indicators (such as the sedimentation or CRP rates), which could lag behind in revealing the existence of underlying inflammation. *Id.* at 61-62, 77-78.

On cross, however, Dr. Tornatore admitted that none of Petitioner's treaters diagnosed him with eosinophilia or directly treated the specific condition, and even seemed to admit that the measurement itself of elevated eosinophil levels was not so out of the normal range to be a red flag. *Id.* at 52 ("an eosinophil count that's slightly elevated does not rise to the level that you would need to treat it, but it is an interesting observation."), 53. Moreover, Dr. Tornatore did not file any medical literature discussing eosinophil counts as evidencing underlying systemic inflammation (or aggravated autoimmunity) or a vaccine reaction.

While stressing the significance of Mr. Maciel's eosinophil blood count percentage, Dr.

[17] Petitioner also filed a number of articles pertaining to the concept of molecular mimicry, a mechanism Dr. Tornatore specifically testified he was not relying on in the present case. Tr. at 54; *see, e.g.*, D. Mason, et al., *A Very High Level of Crossreactivity Is an Essential Feature of the T-Cell Receptor*, 19 Viewpoint: Immunol. Today 395 (1998), filed as Ex. 23 (ECF No. 16-7); M. Oldstone, *Molecular Mimicry, Microbial Infection, and Autoimmune Disease: Evolution of the Concept*, 296 CTMI 1 (2005), filed as Ex. 20 (ECF No. 16-4); F. Noorbakhsh, et al., *Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features*, 26 Neurol. Clin. 759 (2008), filed as Ex. 21 (ECF No. 16-5).

Tornatore was dismissive of the fact that other common indicators of systemic inflammation (including the CRP and ESR rates) did *not* show any evidence of systemic inflammation in Petitioner around the time he received the vaccination (or even thereafter), arguing that it made no sense to him to give those measures more weight than the eosinophil measurements (although he was doing the opposite). Tr. at 61. He further acknowledged that none of Mr. Maciel's treaters deemed any of these indicia of inflammation significant, although he stressed that they were likely more concerned with treating his optic neuritis course. *Id.* at 61-62. Dr. Tornatore also admitted that the medical records showed no sign of any localized reaction to the vaccine (i.e. swelling at the injection site). *Id.* at 62-63. He nevertheless maintained that the elevated eosinophil percentage levels alone could stand as evidence of systemic inflammation, or at least a subclinical reaction to the vaccine. *Id.* at 64.

Apart from the above, Dr. Tornatore also found support for vaccine causation in two articles broadly questioning the medical wisdom of vaccinating MS patients during a relapse. The first article is an undated entry from the National Multiple Sclerosis Society website. Tr. at 19; *Vaccinations: Special Considerations*, Nat'l MS Soc., https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Vaccinations, filed as Ex. 18 (ECF No. 16-2). This article recommends deferring all vaccination during an MS relapse until four to six weeks after onset. Ex. 18 at 1. However, it also notes that certain large-scale epidemiologic studies in Europe (not referenced in the website excerpt) "found no increased risk of developing MS" after receipt of the HPV vaccine. *Id.* at 2. Jeffery also counsels against receiving vaccines during an MS relapse, although it generalizes its recommendation to all vaccines (with emphasis on relapse after receipt of the flu or Hep B vaccines), and did not otherwise discuss the comparative risk posed by the HPV vaccine specifically. *See* Jeffery at 4. At hearing, Dr. Tornatore opined that vaccinating a relapsing MS patient (who is already experiencing some inflammation) "push[es] that [on-going] inflammation even harder." *Id.* at 21.

As to the timing of the exacerbation of Petitioner's MS, Dr. Tornatore maintained that the significant aggravation of his symptoms began the day after receipt of the third HPV dose. Tr. at 28. Dr. Tornatore opined that because Mr. Maciel had already received two doses, he would expect Mr. Maciel to have "a brisker" response to the third. *Id.* In addition, at this point Mr. Maciel's immune system was still recovering from the initial optic neuritis symptoms he experienced in the days before vaccination, rendering it ill-equipped to respond to the stress of additional immunologic activation. *Id.* at 29.

For support, Dr. Tornatore referenced an article from the Institute of Medicine, which in his view, recognizes that a very rapid aggravation can occur in response to a vaccination "if there's been previous exposure."[18] Tr. at 28. He otherwise relied primarily on Owen, which discussed a single case report of MS exacerbation post-Hep A infection within two days of exposure of

[18] Based on a review of the scientific literature filed, it does not appear that Petitioner submitted any article authored by the Institute of Medicine.

antigens via a skin test. Owen at 2307. Given the underlying inflammatory response relating to the MS attack, coupled with the response to the vaccination, Dr. Tornatore concluded it was "easy to imagine" an onset of worsening symptoms within a day. *Id.* at 29. He also allowed for the possibility of a worsening of symptoms within hours, though he acknowledged he knew of no literature supporting that contention. *Id.*

Finally, Dr. Tornatore addressed whether Mr. Maciel's MS was overall worsened by receiving the third HPV dose, answering that question in the affirmative. Tr. at 37. In his estimation, Mr. Maciel would likely have remained symptom-free after the short resolution of his optic neuritis had he not had this final dose, with any lingering sub-clinical inflammation resolving over a period of four to six weeks. Tr. at 25-26, 31. Dr. Tornatore deemed it somewhat speculative to opine as to whether Mr. Maciel would have still experienced an exacerbation similar to the one at issue even in the absence of vaccination, but added that given the largely asymptomatic lesions he was found to have, it was reasonable to assume that his course would not have been as severe. *Id.*at 25. He admitted, however, that since the time of Petitioner's diagnosis he had experienced only a single relapse (although he attributed this to effective treatment rather than as evidence of the mild course of Petitioner's MS). *Id.* at 17-18.

B. *Dr. Adil Javed*

Dr. Javed offered two expert reports and testified on Respondent's behalf at hearing. *See* Report, dated Oct. 14, 2016, filed as Ex. A (ECF No. 22-20) ("First Javed Rep."); Report, dated Apr. 21, 2017, filed as Ex. B (ECF No. 29-1) ("Second Javed Rep.").

Dr. Javed is a board-certified neurologist. *See* Exhibit A, Tab 1, dated Oct. 14, 2016 (ECF No. 22-1) ("Javed CV"). He graduated from Loyola University in Chicago with a bachelor's degree in biology. *Id.* at 2. He subsequently received his medical degree from Southern Illinois University and a Ph.D. in neuroscience from Loyola. *Id.* at 1; Tr. at 81. Thereafter, he completed a residency in the Department of Neurology at Yale University School of Medicine and fellowship in neuroimmunology (with an emphasis on MS) at the University of Chicago. Javed CV at 1; Tr. at 81-82. Since 2007, he has served as an associate professor in the Department of Neurology at the University of Chicago. First Javed Rep. at 1; Tr. at 81. He is also the co-director of the University's Infusion Center, and is responsible for overseeing various immunotherapy treatments administered to patients. Tr. at 83.

Besides research and teaching, Dr. Javed conducts a larger MS clinical practice at the University of Chicago. Tr. at 83. In it, Dr. Javed treats both adult and pediatric patients with MS, NMO, and other autoimmune diseases. *Id.* At hearing, Dr. Javed estimated that he sees roughly 2,200 patients per year, ten percent of whom have MS. *Id.* at 84. And although pediatric MS (meaning patients under the age of 18) is uncommon, he has seen more than 200 such patients, and many generally who presented with optic neuritis. *Id.* He has served as a principal investigator in

a number of multi-national and national MS drug trials. Javed CV at 2; Tr. at 87-88. Dr. Javed has also published a number of articles and book chapters addressing CNS demyelinating diseases (with an MS emphasis). Javed CV at 4-5; Tr. at 83, 85.

Dr. Javed agreed with Dr. Tornatore that Petitioner MS's diagnosis (with initial presenting symptoms related to optic neuritis) was correct, and he also affirmatively placed onset as predating administration of the third dose of HPV vaccine. Tr. at 90, 106, 118. He disputed, however, Petitioner's contention that the HPV vaccine can (or in this case did) cause an exacerbation of Mr. Maciel's symptoms. Rather, Dr. Javed concluded that Petitioner's pre-vaccination symptoms (and course thereafter) proceeded as would be expected in any MS case presenting with optic neuritis, and thus Mr. Maciel could not show that his overall course worsened following receipt of the third dose of the HPV vaccine. First Javed Rep. at 13.

Dr. Javed began his testimony by discussing MS (and its various forms) and its relationship to other neuroinflammatory conditions. He defined MS as an autoimmune disease with an "undertone of neurodegeneration," in which the body's immune cells attack the myelin-producing cells and myelin-constituted proteins that insulate the body's nerve fibers. Tr. at 90; First Javed Rep. at 6. The resulting inflammation damages the myelin and disrupts a nerve's ability to transmit signals, thus causing symptoms similar to those experienced by Mr. Maciel (including loss of visual acuity, headaches, or numbness). First Javed Rep. at 6. Although the cause of MS is unknown, Dr. Javed asserted that it is well accepted that MS can be the product of genetic predisposition, environmental factors (including diet or parasitic infection), viral infections, or a combination of all three. First Javed Rep. at 6-7. Other CNS inflammatory conditions (like TM or optic neuritis) can also be related to an MS course. Optic neuritis (inflammation of the optic nerve), for example, is a presenting symptom of MS in 15-20 percent of MS patients, and 50 percent of all patients with a diagnosis of MS will experience optic neuritis sometime in the course of their disease. *Id.* at 6.

When diagnosing MS, Dr. Javed stressed, reviewing radiologic evidence such as an MRI (which can establish the existence of neurologic injury even in the absence of clinical symptoms), in conjunction with what is known of a patient's clinical course, is highly important. Tr. at 94, 118 ("I will not give an opinion about whether a person has MS or not without any review of MRI"). He referred to instances in which a patient's MRI imaging reveals the presence of CNS lesions in the absence of clinical symptoms as "radiologically isolated syndrome" ("RIS"), while symptoms suggesting the presence of demyelination or inflammation without corroborative MRI evidence constitutes "clinically isolated syndrome" ("CIS"). Tr. at 91-92, 94. An MS diagnosis ultimately hinges on a finding of dissemination of lesions and symptoms in both time (meaning lesions are seen on multiple occasions) and space (i.e. present across multiple locations in the CNS). *Id.* at 102, 119. It is difficult to pinpoint the date prior to clinical presentation when a case of MS actually began. *Id.* at 91. Depending on what is revealed by MRI imaging, a patient's MS could have begun a few weeks

to months before presenting clinical symptoms (given the progressive nature of the disease and the fact that the CNS lesions can be asymptomatic for a period of time). *Id.* at 91, 93.

Dr. Javed agreed that a traditional MS course (while often unpredictable) can include relapses after the presenting clinical event. Tr. at 98; First Javed Rep. at 6. Dr. Javed defined an MS relapse as "an attack" or a "flare" (characterized by some "clinical symptom" or worsening of symptoms) lasting anywhere from twenty-four hours to several weeks. First Javed Rep. at 6; Tr. at 98. According to Dr. Javed, the most common trigger for relapse is an underlying infection, as a recurrence is evidence of ongoing inflammation and/or an immune system response. Tr. at 98, 101, 169. However, he acknowledged that a live virus vaccine could also initiate a relapse (given the accompanying inflammatory response typically experienced). *Id.* `

As to a flare's pathogenesis, Dr. Javed disputed the contention that flares are caused only by environmental factors external to the CNS. Tr. at 101. Rather, an MS relapse can be wholly independent of peripheral involvement – and can even originate in the brain. *Id.* at 101-02. He opined that immune cells can gather near the vasculature "cuff" and use cytokine communication to impair nerve function (absent any underlying inflammation). *Id.* at 102-03. In support, Dr. Javed referenced the presence of oligoclonal bands (which corroborate dissemination in time and space) as evidence that immune cells "have already taken up residence in the brain" and are propagating the inflammatory processes necessary to cause a flare on their own. *Id.*

Dr. Javed opined that relapses can occur in a timeframe of once a year or more frequently depending on the patient's overall disease trajectory. Tr. at 98-99, 100; First Javed Rep. at 6. The length of a relapse is unpredictable, although Dr. Javed estimated that a typical recovery period post-relapse could last ten weeks. *Id.* at 98. Of particular relevance herein, he contended that any symptoms seen within thirty days of the start of a flare or relapse are considered to be clinically associated with the same flare/relapse. *Id.* at 103-04. In light of the above, Dr. Javed explained that in his practice, he would routinely monitor a relapsing MS patient for a month or more to determine if that patient was experiencing a true relapse or "pseudo-relapse (meaning only a "small fluctuation" of milder symptoms still connected to the initial relapse). *Id.* at 99-101.

Upon review of Mr. Maciel's MRI imaging results, Dr. Javed concluded (as did Dr. Tornatore) that Petitioner was correctly diagnosed with MS given the presence of chronic, nonenhancing lesions in multiple locations in the brain (as well as his clinical presentation). Tr. at 119-20; First Javed Rep. at 6; Second Javed Rep. at 3. He also agreed with Dr. Tornatore that Mr. Maciel's symptoms (including blurred vision and headaches) began prior to his third dose of the HPV vaccine around March 3, 2014. Tr. at 104-06, 113; First Javed Rep. at 10. He disputed, however, Dr. Tornatore's interpretation of Petitioner's clinical course.

In particular, Dr. Javed took issue with Dr. Tornatore's assertion that Mr. Maciel's pre-vaccination optic neuritis symptoms had *entirely* resolved prior to receipt of the third dose of HPV. Tr. at 108, 179. According to Dr. Javed, a typical optic neuritis course would not reach nadir and then completely resolve within a twenty-four hour period. *Id.* at 108. Rather, and in light of general review of the medical record as a whole, Dr. Javed concluded that Mr. Maciel's symptoms in the days before and after the third HPV vaccine dose were best categorized as a *single* MS flare presenting as optic neuritis, rather than two separate and distinct flares. *Id.* at 113.

Part of Dr. Javed's opinion turned on his characterization of Mr. Maciel's optic neuritis, a condition he defined as inflammation of the optic nerve, resulting in vision problems and pain. Tr. at 104. Pain associated with acute optic neuritis can be exacerbated by eye movement as well as optic disc swelling. *Id.* at 106. He deemed Petitioner's neuritis to be "retrobulbar"[19] – meaning inflammation was occurring at the back of the eyeball. Tr. at 105-06. Dr. Javed opined that this would result in somewhat less pain overall (given the inflammation's location near the disc or papilla region of the eye). *Id.* at 104, 105-06; Ex. 13 at 107. Based on his reading of the record, Dr. Javed proposed that Mr. Maciel's symptoms likely reached nadir around March 9, 2018, then gradually resolved in the months following his treatment. Tr. at 116, 123 ("[f]rom March to July, in about fourth months, I would say he did pretty good") (citing Ex. 13 at 107). Mr. Maciel's treaters also considered his symptoms (as a whole) to be progressive in nature, rather than separate flares. *Id.* at 113-14 (citing Ex. 13 at 114 (noting "one week history" of "intermittent but progressive" symptoms since 3/3/2014)); Javed Second Rep. at 3.

In support of his opinion concerning the scope of Petitioner's initial MS flare, Dr. Javed spent some time at hearing discussing the usual nature of optic neuritis's course. Pediatric optic neuritis akin to what Petitioner would have experienced most commonly results in a more severe course (i.e. bilateral swelling and severe loss of vision) than what adult patients experience, though injury to the optic nerve is easier to detect. *Id.* at 110. Although pediatric optic neuritis is readily treatable, children do not attain 100 percent visual acuity even following a full recovery. *Id.* at 111-12. Based on his clinical experience, Dr. Javed opined that a good recovery results in increased vision of, at best, 20/40 vision in six months. *Id.* at 107-08.

Based on the above, Dr. Javed maintained (as noted above) that the course of a typical pediatric case of optic neuritis would not proceed as Dr. Tornatore suggested, completely resolving within days but then immediately recurring after vaccination. Dr. Javed stated that he had never in his career treated or diagnosed a patient with optic neuritis who reached nadir and then recovered within two days. Tr. at 107-08. At best, an intermittent course of optic neuritis featuring ups and downs might include a "pseudo-relapse" (triggered by temperature change or fever, for example). *Id.* By contrast, a "real relapse" of optic neuritis initiated by an inflammatory-driven process would not resolve in a period of days. *Id.* at 109. Thus, in light of both the scientific literature offered and

[19] "Retrobulbar" refers to the posterior of the eyeball. *Dorland's* at 1635.

his clinical practice experience, Dr. Javed could not find support for Dr. Tornatore's theory that Mr. Maciel experienced an episode of optic neuritis pre-vaccination that *entirely* resolved within days – and thereafter, suffered a separate and distinct *second* flare post-vaccination.

In so maintaining, Dr. Javed relied primarily on a single item of literature. *See* L. Balcer, *Optic Neuritis*, 354 N. Eng. J. Med. 1273 (2006), filed as Ex. A, Tab 2 (ECF No. 22-2) ("Balcer"). Balcer is a case report involving a patient presenting with optic neuritis beginning one week prior to medical presentation. Balcer at 1273. The study cites multiple pieces of literature confirming that acute optic neuritis can progress "over a period of hours to days (maximum ten days)" with recovery beginning "within 2 to 4 weeks" following onset. *Id.* at 1274. At hearing, Dr. Javed opined that Balcer reflects a typical optic neuritis course (and recovery) based on the accepted view in the medical community and as supported by the scientific literature. Tr. at 107-08. Balcer also confirms Dr. Javed's point that pediatric optic neuritis was more likely to be severe in nature, underscoring his contention that it would not resolve in the manner proposed by Petitioner's causation theory. *Id.* at 110.

Dr. Javed similarly disputed the sufficiency of Petitioner's evidence supporting his contention that the HPV vaccine could exacerbate MS (thereby causing a relapse). A viral infection or live viral vaccine – either of which could greatly activate a systemic inflammatory response – would be more likely to trigger a response in an individual already experiencing an immune response to MS. Tr. at 147, 149. An inactivated vaccine, on the other hand, like the HPV vaccine[20] is distinguishable in its lessened ability to promote inflammation (especially in the absence of evidence that the vaccine in this case caused a systemic localized reaction, for example, swelling at the injection site or sore arm), thus reducing the likelihood that such a vaccine could exacerbate existing inflammation. *Id.* at 147-48.

To support this aspect of his opinion, Dr. Javed offered various large-scale studies evaluating the relative risk of developing vaccine-related MS following HPV vaccination.[21] First Javed Rep. at 8-9; Second Javed Rep. at 4-5; Tr. at 139-47. One cohort study examined over 700,000 female patients receiving the HPV vaccine in Denmark and Sweden between 2006-13. *See* N. Scheller, et al., *Quadrivalent HPV Vaccination and Risk of Multiple Sclerosis and Other Demyelinating*

[20] The HPV (Gardasil) vaccine is a non-infectious, recombinant quadrivalent vaccine. *See Package Insert*, FDA, Apr. 2015, https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf (last accessed on Sept. 25, 2018). It contains purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18 (and thus, is not considered live-attenuated). *Id.* The remainder of the vaccine is comprised of aluminum (an amorphous aluminum hydroxphosphate sulfate adjuvant), sodium chloride, L-histine, polysorbate, yeast protein, and water. *Id.*

[21] Dr. Javed lacks direct expertise in epidemiologic matters. Tr. at 163. Accordingly, the inclusion of such evidence in his trial presentation does not gain added heft simply because he mentioned them or curated the offered items of literature (assuming he did so). At the same time, however, such items have their *own* individual probative value, and I have considered them in that manner (just as I consider pieces of medical or scientific literature filed by petitioners even when their own experts lack a grounding in the subject matter of a particular item).

Diseases of the Central Nervous System, 313 JAMA 54 (2015), filed as Ex. E (ECF No. 35-3) ("Scheller"). Scheller found no associated increase of onset of MS (or any other demyelinating disease) post-vaccination after receipt of the HPV vaccine. *Id.* at 54, 59-60; *see also* S. Tanday, *HPV Vaccination Not Linked to Multiple Sclerosis*, 16 Lancet E57 (2015), http://doi.org/10.1016/S1470-2045(14)71194-5, filed as Ex. A, Tab 12 (ECF No. 22-12) (reviewing the Scheller study and affirming its conclusion). In addition, Dr. Javed referenced a French case-control study of roughly 1,800 patients (22 percent of whom had received the HPV vaccine) that also found no association between the HPV vaccine and autoimmune illnesses (including MS). *See* L. Grimaldi-Bensouda et al., *Risk of Autoimmune Diseases, and Human Papilloma Virus (HPV) Vaccines: Six Years of Case-Referent Surveillance*, 79 J. Autoimmun. 84 (2017), filed as Ex. C (ECF No. 35-1) ("Grimaldi-Bensouda"). Indeed – in Dr. Javed's reading, Grimaldi-Bensouda seemed to suggest that the risk of MS after receipt of the HPV vaccine was *reduced* rather than increased. Tr. at 138-39; Grimaldi-Bensouda at 4. He did, however, acknowledge that (consistent with the National MS Society guidance highlighted by Dr. Tornatore) patients in the midst of a "serious" MS relapse should not be vaccinated. *Id.* at 146, 167.

Additional articles offered by Dr. Javed reached similar conclusions. *See, e.g.*, S. 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 Ex. D (ECF No. 35-2) ("Miranda") (French case-control study of over two million female patients, 37 percent of whom received the HPV vaccine, and finding no increase in CNS demyelinating disease following exposure to the vaccine); C. Chao, et al., *Surveillance of Autoimmune Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine*, 271 J. Int. Med. 193 (2011), filed as Ex. F (ECF No. 35-4) ("Chao") (case review of over 100,00 HPV-recipients in the United States, finding no increase in MS post-vaccination).

Only one article offered by Respondent addressed the potential effect of vaccines on an existing course of MS, or their propensity to spark flares. *See* M. Mailand, et al., *Vaccines and Multiple Sclerosis: A Systematic Review*, 264 J. Neuro. 1 (2017), filed as Ex. A, Tab 10 (ECF No. 22-10) ("Mailand"). Mailand is a review article that cataloged the existing scientific evidence concerning vaccinations and the development of MS and MS relapses. It references five studies (some of which have been filed as evidence in the present matter) that document no increased risk of MS following receipt of the HPV vaccine. Mailand at 4 (referencing Scheller, Grimaldi-Bensouda, and Chao). However, the majority of the discussion in Mailand regarding the scientific evidence supporting a vaccine-induced MS relapse relates only to the H1N1 flu vaccine. *Id.* at 13. Mailand nevertheless concludes that the HPV vaccine "does not seem to increase the risk of developing MS[,] . . . ." *Id.* at 14.

Although Dr. Javed did not dispute that Mr. Maciel displayed significant and concerning MS symptoms post-vaccination, he questioned whether the *overall* post-vaccination course reflected an

alarming worsening of his condition attributable to the third HPV vaccine dose. Tr. at 150.[22] He did not accept Petitioner's assertion that he had completely recovered by the date of his final HPV vaccine dose. *Id.* at 172. He also pointed out that none of Mr. Maciel's treaters expressed the view that the Petitioner had experienced two separate flare events around the time of vaccination, noting that treaters like Dr. Hyslop viewed Petitioner's course as progressive, if intermittent. *Id.* at 113-15. In this reading of the record, Mr. Maciel actually did not reach nadir until March 9th. *Id.* at 116-17, citing Ex. 13 at 107.

Dr. Javed thus categorized Petitioner's symptoms as consistent with "the natural course" of an MS-related flare presenting as optic neuritis. Tr. at 150. In his view, Mr. Maciel's course was consistent with what a typical MS patient would likely experience in a relapse (and recovery thereafter), and thus revealed no evidence of an "aggravation from the natural course." *Id.* at 152. To support this contention, Dr. Javed referenced specific symptoms documented in Petitioner's medical record, such as his demonstrated loss of visual acuity and the MRI evidence. *Id.* at 149-51.[23] He also emphasized how Mr. Maciel's clinical experience was consistent with Balcer's discussion of the expected course for optic neuritis. *See* Balcer at 2 (categorizing optic neuritis as an acute progression over a period of hours to days, with recovery beginning two to four weeks post-onset). Despite acknowledging throughout the course of his testimony that MS is unpredictable in nature, Dr. Javed concluded that, taken as a whole, Mr. Maciel's course did not deviate from the norm. *Id.* at 149, 152, 165. Indeed – he expressed the view that his course was overall *better* than he would have expected. *Id.* at 112, 123.

As to the timeframe proffered by Petitioner, Dr. Javed disputed that there was reliable scientific evidence establishing that the HPV vaccine could, in a one-day window, cause or aggravate preexisting MS. Tr. at 152-53. Owen (cited by Dr. Tornatore), for example, involved the direct injection of skin tests antigens (including candidin, staphage, and mixed respiratory vaccine antigens), all of which are distinguishable from the viral antigens contained in the HPV vaccine, and which would logically induce a prompt inflammatory response. *Id.* at 133-36; Owen at 2308. He thus deemed Owen entirely inapplicable to the present matter given the differences in antigenic stimulation and pre-inoculation health history. *Id.* at 135.

Besides highlighting literature tending to rebut any association between the HPV vaccine and MS exacerbation, Dr. Javed attempted to refute Dr. Tornatore's argument that increased levels of eosinophils were evidence of an underlying systematic inflammatory process. Tr. at 124-27; First

[22] Dr. Javed did express some reluctance to predict what *any* individual's likely course of MS would be. Tr. at 100, 149, 165.

[23] Dr. Javed in fact felt that the MRI evidence was strong enough that he would have treated Petitioner as actively suffering from an MS flare even if it were incontrovertibly the case that his initial optic neuritis had resolved on March 6th as Petitioner contends. Tr. at 166-67.

Javed Rep. at 11-12; Second Javed Rep. at 4. He began by asserting that eosinophil levels were a somewhat "nonspecific response" not viewed as an MS marker (as Dr. Tornatore admitted), and that could instead simply reflect the existence of seasonal allergies[24] or dietary changes. Tr. at 129. But Dr. Javed also questioned Dr. Tornatore's measurement rubric, placing more weight on the white blood cell total differential count than the percentage reference range in determining whether a patient's eosinophil levels are abnormal. Tr. at 124, 125-26. He offered medical literature to support this contention. *See* C. Curry, et al., *Differential Blood Count: Interpretation*, Medscape, Jan. 14, 2015, https://emedicine.medscape.com/article/2085133-overview, filed as Ex. B, Tab 1 (ECF No. 29-2) ("Curry"). Curry specifically categorizes relative percentage count as "misleading," concluding instead that an absolute count produces more meaningful information when interpreting a reference range. *Id.* Percentage counts can fluctuate based upon a variety of factors (such as age, gender, and race), and thus should not be considered "rigid determinants" in assessing evidence of an increase. Tr. at 127.

Dr. Javed also asserted that Petitioner's lab results did not reflect the existence of inflammation restimulated by the third HPV vaccine dose. Tr. at 130-36. He noted that Petitioner's ESR rate and CRP rate were both better indicators of any underlying inflammation in Mr. Maciel's body than eosinophil levels. *Id.* at 130. Dr. Javed in particular characterized the CRP rate as a more "sensitive measure for [a] systemic inflammatory response," as it can rise and fall within a twenty-four hour period. *Id.* at 131. But Petitioner's lab testing relating to both his ESR and CRP rates returned normal results, suggesting that he was not experiencing systemic inflammation at the time of the vaccination (or thereafter). *Id.* at 130-31 (citing Ex. 14 at 102). Such test results would have been positive if a patient wer experiencing the level of vaccine reaction Petitioner alleges the HPV vaccine induced in him. *Id.* at 148.

IV. Procedural History

As noted above, this case was initiated in April 2015. Petitioner subsequently filed relevant medical records, concluding the process at the end of July 2015 with the Statement of Completion. ECF No. 11. Respondent's Rule 4(c) Report was thereafter filed on October 9, 2015 (ECF No. 12), and in it Respondent challenged the appropriateness of an entitlement award. The case thereafter proceeded in a timely manner.

Petitioner's first expert report from Dr. Tornatore was filed the following spring, on April 26, 2016 (ECF No. 17-2). Respondent filed a responsive report from Dr. Javed on October 14, 2016 (ECF No. 22-20). The following January 2017, Petitioner responded with Dr. Tornatore's second expert report (ECF No. 23-2), and Respondent filed Dr. Javed's supplemental report on

[24] Dr. Javed acknowledged that seasonal allergies are not commonly associated with MS flares (a point also emphasized by Dr. Tornatore), though he still maintained that eosinophilia was not a reliable indicator for the presence of an autoimmune process . Tr. at 129.

April 21, 2017 (ECF No. 29-1). The parties next agreed that the matter was ready for hearing, and I set it down to be tried in March 2018. *See* Prehearing Order, dated April 10, 2017 (ECF No. 28). The hearing went forward as scheduled and included testimony from the experts identified above. Petitioner offered no fact witnesses in support of his claim. The parties opted not to submit post-hearing briefs, and the matter is now ripe for decision.

V. Applicable Law

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[25] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

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

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

Circuit in *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005): "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

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

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017).

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

(Fed. Cir. 2013) (citations omitted); *Tarsell*, 133 Fed. Cl. at 793 (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance).

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

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant

vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Standards Applicable to Significant Aggravation Claim*

In this matter, Petitioner maintains that the third HPV vaccine dose he received in March 2014 significantly aggravated his then-existing MS. Where a petitioner so alleges, the *Althen* test is expanded, and the petitioner has additional evidentiary burdens to satisfy. *See generally Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (2009). In *Loving*, the Court of Federal Claims combined the *Althen* test with the test from *Whitecotton v. Sec'y of Health & Human Servs*., 81 F.3d 1099, 1107 (Fed. Cir. 1996), which related to on-Table significant aggravation cases. The resultant "significant aggravation" test has six components, which are:

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

Loving, 86 Fed. Cl. at 144; *see also W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims"). In effect, the last three prongs of the Loving test correspond to the three sole *Althen* prongs.

Subsumed within the *Loving* analysis is the requirement to evaluate the likely natural course of an injured party's preexisting disease, in order to determine whether the vaccine made the petitioner worse than he would have been but for the vaccination. *Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381-82 (Fed. Cir. 2012) (upholding special master's determination that petitioner had failed to carry her burden of proof in establishing that her preexisting injury was worsened by the relevant vaccine); *Hennessey v. Sec'y of Health & Human Servs.*, No. 01-190V, 2009 WL 1709053, at *41-42 (Fed. Cl. Spec. Mstr. May 29, 2009), *mot. for review den'd*, 91 Fed. Cl 126 (2010). The critical point of examination is thus "whether the change for the worse in [petitioner's] clinical presentation was aggravation or a natural progression" of the underlying

condition. *Hennessey,* 2009 WL 1709053, at *42.[26] The Federal Circuit has upheld the determinations of special masters that worsening was not demonstrated by a petitioner in connection with establishing her overall preponderant burden of proof for a non-Table causation-in-fact claim. *See, e.g., Snyder/Harris v. Sec'y of Health & Human Servs.,* 553 F. App'x 994, 999-1000 (Fed. Cir. 2014); *Locane,* 685 F.3d at 1381-82.[27]

Application of *Loving's* "worsening" requirement has been the occasion for some disparate holdings by special masters as well as the Court, especially due to the problems posed when evaluating the impact of a preexisting genetic condition that likely played *some* role in an injured party's post-vaccination health. In some cases, the mere fact that an injured party was literally "worse" than she was immediately prior to the vaccination at issue has been viewed as sufficient to satisfy this prong. *See, e.g., Williams v. Sec'y of Health & Human Servs.*, No.04-1725V, 2007 WL 2775190, at *27 (Fed. Cl. Spec. Mstr. Sept. 11, 2007).

In other instances, however, the mere fact a vaccine might "trigger" a transient negative response in an individual with an underlying condition has not been deemed proof of worsening if that individual's overall expected course would not be different. *Faoro v. Sec'y of Health &Human Servs.*, No. 10-704V, 2016 WL 675491, at *27 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. rev. den'd*, 128 Fed. Cl. 61 (Fed. Cl. Apr. 11, 2016) (finding that "the vaccinations would not have changed her clinical course, and thus the vaccinations did not significantly aggravate her preexisting condition"). This point has been emphasized in a subcategory of Program cases involving the claim that a child's Dravet syndrome (a condition known to be associated with a particular genetic mutation) was significantly aggravated by vaccination. *Faoro*, 2016 WL 675491, at *1. In such cases, special masters have repeatedly determined that petitioners failed to show that the child's expected outcome would have been different but for the vaccination – even though it was undisputed that the child's first major seizure may have been triggered by vaccination. *Id.* at *2 ("[a]lthough H.E.F.'s vaccinations may have caused a low-grade fever or otherwise triggered her first seizure, neither the initial seizure nor her vaccinations caused or

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

[27] This is consistent with the fact (well recognized by controlling precedent) that evidence of "worsening" relevant to Respondent's alternative cause burden may also by evaluated by a special master in determining the success of a petitioner's initial, prima facie showing. *Snyder/Harris,* 553 F. App'x at 1000, *quoting Stone,* 676 F.3d at 1380 ("no evidence should be embargoed from the special master's consideration simply because it is also relevant to another inquiry under the statute"); *see also de Bazan v. Sec'y of Health & Human Servs.,* 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("[t]he government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief").

significantly aggravated her Dravet syndrome and resulting neurological complications"); *see also Snyder/Harris*, 553 F. App'x at 994 (special master was not arbitrary in finding that petitioners' expert failed to show that the child's outcome would have been different had he not received the vaccinations at issue).

C. *Law Governing Analysis of Fact Evidence*

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

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

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical

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

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

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

D. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509

U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

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

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 91997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

E. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all of the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case – just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to – and likely undermines – the conclusion that it was not considered").

ANALYSIS

I. Overview of Relevant Medical Concepts and Prior Related Decisions

The parties' experts agreed largely on the proper definition of MS and what kind of clinical or radiologic evidence establishes its existence. As Program case law recognizes, MS is categorized as a demyelinating central nervous system disease. *See Taylor v. Sec'y of Health & Human Servs.*, No. 13-700V, 2018 WL 2050857, at *21 (Fed. Cl. Spec. Mstr. Mar. 9, 2018). Patients diagnosed with MS typically experience multiple episodes of CNS demyelination separated in time and space, evidencing a more progressive decline in their overall health course. *Id.* An MRI can be used to corroborate the dissemination in space and time requirement, and often reveals old lesions as well as enhancing/new lesions. *Id.* Evidence of oligoclonal bands in cerebrospinal fluid testing (which reveal brain inflammation) is also frequently seen in patients with MS. *Id.* Symptoms can include numbness or weakness in the body, loss of vision, tremors, unsteady gait, slurred speech, and dizziness. *Id.* The demyelination that results in MS is believed autoimmune in nature (although the triggers of that autoimmunity are not fully understood). C. Tur, et al., *Early Accurate Diagnosis Crucial in Multiple Sclerosis*, 259 Practitioner 21-27, at 21 (Sept. 2015), filed as Ex. A, Tab 3 (ECF No. 22-3); Tr. at 90 (Dr. Javed characterizing MS as likely an autoimmune disease).

Other Program claimants have attempted to argue that different vaccines significantly aggravated a person's preexisting MS, to varying degrees of success. *See, e.g., Quackenbush-Baker v. Sec'y of Health & Human Servs.*, No. 14-1000V, 2018 WL 1704523 (Fed. Cl. Spec. Mstr. Mar. 14, 2018) (flu vaccine significantly aggravated the petitioner's preexisting MS); *W.C. v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 440 (2011) (upholding special master's determination that flu vaccine did not significantly aggravate preexisting MS), *aff'd*, 704 F.3d 1352 (Fed. Cir. 2013); *Bubb v. Sec'y of Health & Human Servs.*, No. 01-721V, 2005 WL 1025707 (Fed. Cl. Spec. Mstr.

Apr. 29, 2005) (tetanus toxoid vaccine did not significantly aggravate preexisting MS). None of these decisions are completely on point, but they nevertheless provide some guidance in addressing the claim at hand.

In *W.C.*, the claimant alleged that the flu vaccine aggravated his previously-asymptomatic MS (with onset about 12 days after vaccination), but the special master responsible for the case denied entitlement. The Court of Federal Claims upheld the special master's determination, but in doing so was careful to note that factually and scientifically, the case presented some close calls that could have been decided by a different special master with the opposite result, and thus the underlying decision was upheld mainly as a function of applying the review standards. *W.C.,* 100 Fed. Cl. at 456 (noting that although that the evidence was "so closely balanced that the decision could have gone either way," nevertheless "the court cannot say that the special master's findings were arbitrary").

Bubb stands as a stronger endorsement of the case *against* an association between vaccines and MS exacerbation than *W.C.* There (as here), it was undisputed that the petitioner suffered from MS prior to vaccination. *Bubb,* 2005 WL 1025707, at *2. In addition, the record supported the conclusion that not only had the petitioner experienced a post-vaccination flare, but that the relapse resulted in a sufficiently severe worsening of her condition to constitute a "significant aggravation" under the Act. *Id.* at *22. Nevertheless, the special master decided the claim against the petitioner, largely due to her inability to connect the relevant vaccination to her MS worsening. *Id.* at *24. The special master was especially persuaded by literature offered by Respondent to rebut any purported association between vaccination and MS exacerbation. I*d.* at *20-21, 24. This, in addition to the lack of other probative evidence relating exacerbation to the vaccine (such as the views of contemporaneous treaters), resulted in the denial of entitlement.

In *Quackenbush-Baker*, by contrast, a petitioner succeeded in establishing that the flu vaccine significantly aggravated her MS. However, the petitioner's MS was wholly asymptomatic prior to vaccination, and thus deemed to have preexisted solely on the basis of MRI evidence. *Quackenbush-Baker*, 2018 WL 1704523, at *8. The asymptomatic, RIS nature of petitioner's MS seems to have factored heavily in the special master's finding in petitioner's favor. *Id.* at *14-15. It also appears that the scientific evidence deemed so persuasive in *Bubb* on the question of a vaccine's capacity to exacerbate MS was not offered by the experts in *Quackenbush-Baker*. *Id.* at *15-17.

The experts in this case disagreed to some extent about the typical course of optic neuritis (which can be a presenting symptom for MS) and its most likely resolution. Optic neuritis is defined as "inflammation of the optic nerve." *Dorland's Illustrated Medical Dictionary* 1252 (32nd ed. 2012). Acute demyelinating optic neuritis is the presenting clinical feature in 15-20 percent of patients diagnosed with MS, and 50 percent of MS patients will experience optic neuritis

during their disease course. Balcer at 1273. A clinical diagnosis of optic neuritis is made based on a patient's health history and clinical history (with vision loss and eye pain upon movement as primary symptoms). *Id.* at 1274. Optic neuritis's symptoms typically progress to nadir over a period of hours to days, and recovery of visual acuity begins two to four weeks following onset. *Id.* Acute optic neuritis in children can differ from the typical adult form. *Id.* at 1278. Optic-disc swelling and bilateral disease are more common in children, as is severe vision loss (20/200 or worse in 84 percent of cases). *Id.* While it is possible for adult patients to recover normal vision, children typically recover visual acuity of 20/40 or better. *Id.*

II. Petitioner's Direct Causation Claim Lacks Evidentiary Support

Although Dr. Tornatore's expert report suggested that Mr. Maciel's symptoms could have been triggered by the third dose of the HPV vaccine, at hearing Dr. Tornatore acknowledged that it was reasonable to conclude from the medical record that Mr. Maciel's optic neuritis – the presenting symptom of his MS – *predated* his receipt of the third dose of the HPV vaccine. *See, e.g.*, Tr. at 11-12, 47-49, 75-76. Dr. Javed made similar assertions. *Id.* at 90, 106, 118; First Javed Rep. at 12. Both views were based on record evidence of pre-vaccination neurologic symptoms as documented by Mr. Maciel's treating physicians, as well as the subsequent MRI results. Neither expert proposed (or in Dr. Javed's case, conceded) that the two earlier HPV vaccine doses initiated Mr. Maciel's MS (and statements to the contrary in the affidavits submitted in support of this claim are not a sufficient evidentiary basis for an entitlement finding unless corroborated with *other* reliable scientific or medical evidence).[28]

After consideration of the same evidence plus expert testimony, I find as well that the medical record best supports the conclusion that Petitioner's MS/optic neuritis began *before* the his receipt of the third HPV dose on March 6, 2014 – and was not caused by the earlier two doses either. Mr. Maciel's medical records persuasively establish that his optic neuritis symptoms began pre-vaccination, around March 3, 2014. The radiologic evidence also bulwarks this conclusion. MRIs performed on Mr. Maciel revealed sufficient amounts of lesions disseminated in time and space to corroborate (with Petitioner's clinical presentation) an MS diagnosis. It is highly likely that these lesions predated vaccination by some amount of time.

Based on this determination, Petitioner's direct causation claim cannot succeed. *See, e.g.*, *Locane v. Sec'y of Health & Human Servs.*, 99 Fed. Cl. 715 (2011) (petitioner's alleged vaccine-induced injury began prior to her vaccinations and therefore vaccine causation could not be established), *aff'd*, 685 F.3d 1375 (Fed. Cir. 2012); *W.C.*, 100 Fed. Cl. at 453 (upholding special

[28] Petitioner's pre-hearing brief couches his claim as one of direct causation, but then seems to admit that the claim is better understood as one of significant aggravation. *See, e.g.*, Pre-Hearing Memorandum, dated January 16, 2018 (ECF No. 31), at 17 ("the vaccine significantly aggravated the autoimmunity which was present prior to his receipt of the third HPV vaccination").

master's denial of direct causation claim where petitioner's medical records suggested lesions developed pre-vaccination). I therefore will turn to Petitioner's remaining claim: that the third HPV vaccine dose significantly aggravated Petitioner's MS/optic neuritis. I address the most relevant *Loving* factors in order of their importance to my overall determination.[29]

III. Petitioner Has Not Offered Preponderant Evidence Supporting his Significant Aggravation Claim

A. *Petitioner's Post-Vaccination Symptoms Constituted a Single MS Flare Predating His Receipt of the Third HPV Vaccine Dose*

A central component of Petitioner's significant aggravation claim requires resolution of a fact dispute: whether Petitioner's optic neuritis (beginning on March 3, 2014) continued through the time of his receipt of the third HPV dose three days later, or had resolved completely (at least from a clinical/symptomatic perspective), with a subsequent, independent MS flare beginning immediately upon the heels of that final HPV vaccine dose (and which, Petitioner argues, was caused by that vaccination). Although Petitioner does not deny that his MS likely already existed at the time of the final dose, he maintains that he experienced two separate flares (although he maintains that the first resulted in residual, if subclinical, inflammation that was negatively affected by receipt of the HPV vaccine).

The evidence does not preponderate in Petitioner's favor on this fact issue. Rather, the record best establishes that Petitioner's optic neuritis had not completely resolved by the date of his receipt of the third HPV dose, and therefore the symptoms experienced before and after vaccination were all part of a single flare. My conclusion finds support in the medical history, as understood by existing medical views on the character and course of optic neuritis.

Respondent persuasively established that optic neuritis commonly does not resolve quickly, especially the pediatric version (which it is reasonable to attribute Petitioner as having experienced despite the fact that he was a teenager at the time). Rather, it is characterized by a slow recovery before baseline health (and, in particular, visual acuity) is again attained. Tr. at 107-

[29] I do not address *all* of the *Loving* prongs, however, for the simple reason that Petitioner's failure to establish linchpin elements of his claim (in particular, that he experienced an MS exacerbation, or that the HPV vaccine could exacerbate his MS) renders a rote determination of Petitioner's success in establishing each individualized prong unnecessary. *See, e.g., Bigbee v. Sec'y of Health & Human Servs.*, No. 06-663V, 2012 WL 1237759, at *36 (Fed. Cl. Spec. Mstr. Mar. 22, 2012) (citing *Althen*, 418 F.3d at 1278). Had I done so, however, I would find the following (a) Mr. Maciel was experiencing his first clinical symptom of MS before his March 6, 2014 final HPV vaccine dose (first *Loving* prong), (b) he currently suffers from MS although it appears his treatment has been effective in managing symptoms (second *Loving* prong), (c) the final HPV dose did not cause any aggravation of his MS (fifth *Loving* prong), but (d) the timing in which the aggravation is alleged to have occurred was medically appropriate given Petitioner's theory (although I do not find the theory otherwise plausible given the lack of reliable science supporting it) (sixth *Loving* prong).

08, 111-12. As confirmed by Balcer, optic neuritis progresses over hours to days, with recovery usually no sooner than two to four weeks after onset. Balcer at 1274. In addition, Respondent persuasively established that individual MS flares generally last more than a few days – and are also usually separated in time by weeks or more before they are deemed to reflect a new flare. *See* First Javed Rep. at 6; Tr. at 98-99, 103-04.

Keeping the above in mind, the medical record in this case provides many grounds for viewing Petitioner's optic neuritis as a single, initial MS flare beginning March 3, 2014. The most compelling evidence in support of this conclusion is the overall nature of symptoms Mr. Maciel experienced. Both before and after receipt of the last HPV dose, the records suggest that his symptoms were broadly intermittent – not that they resolved completely pre-vaccination only to return in a more severe form. His pre-vaccination headache, for example, was initially mild enough to be treated with over-the-counter pain relievers (e.g., Ex. 14 at 112) – and even *after* recurrence, the pain was similarly alleviated, thus underscoring a connection between pre and post-vaccination symptoms rather than clean break. *See, e.g.*, Ex. 13 at 501-02. Also significant is the fact that no treater appears to have viewed the two headache incidents as distinct, instead comprehending them as part of the same progressive continuum. *See, e.g.*, Ex. 13 at 114 ("[s]ymptoms began on 3/3/14 intermittently and *became progressively worse* over the week" (emphasis added)).

In addition, Petitioner and/or his parents consistently informed treaters that his presenting symptoms as of March 8, 2014, had begun about a week before (meaning prior to vaccination). *See, e.g.*, Ex. 14 at 68, 114, 135. While such treaters were also told that the initial headaches Petitioner experienced had "resolved," the overall impression from these records is that the symptoms that led Mr. Maciel to seek emergency medical treatment constituted an ongoing, if halting, course of symptoms. The compressed timeframe (a little more than a week, as opposed to a month or more) is also consistent with that reading, with the period in which Petitioner's symptoms were in remission too short to draw the conclusions urged by Dr. Tornatore.[30] All in all, the evidence suggests it is more likely than not that Petitioner's optic neuritis lasted longer than a few days, and bridged the pre and post-vaccination period.

B. *Petitioner did not Experience an Overall Worsening of his MS Course After Receipt of the Third Dose of HPV Vaccine*

Although the above factual determination is unhelpful to Petitioner's claim, it does not preclude the conclusion that the HPV vaccine could have worsened his overall MS course *otherwise* – not by provoking a second flare, but instead by exacerbating the existing optic neuritis/initial MS flare. But Petitioner has not demonstrated this preponderantly either.

[30] Dr. Tornatore's argument about the risks of vaccination during an MS flare – a medically-reliable point that even Dr. Javed had trouble disputing – also contains the tacit admission that Petitioner was experiencing only a single flare still ongoing, if progressing intermittently, at the time of vaccination. Tr. at 19, 21.

First, the medical record does not suggest that Mr. Maciel's MS/optic neuritis course was notably worse than what would be expected for an individual suffering from MS who received no vaccine. Although Petitioner's preexisting optic neuritis had progressed post-vaccination to the point where he reasonably sought medical intervention, the intermittent vector of its development was already in a progressively worse direction. Thereafter, Mr. Maciel experienced only a single additional optic neuritis flare in May 2014, and since then appears to have received effective treatment sufficient to maintain a baseline level of health (although given the disease, additional relapses are possible).This course is consistent with Dr. Javed's characterization – that it is not distinguishable in severity from what other MS patients he has treated would experience (and could even be interpreted to have been *less* severe). Tr. at 165. The records also do not contain treater observations or opinions that could be credibly marshalled as endorsing the view that the overall severity of Mr. Maciel's MS exceeds what would be expected in the majority of cases.

Second, the medical records do not corroborate Petitioner's contention (reflected in a portion of Dr. Tornatore's testimony) that Mr. Maciel was experiencing a systemic immune response after receipt of the third HPV vaccine dose (thus providing circumstantial evidence that an immune-stimulated process attributable to vaccination was contributing to his disease course). Those records set forth no documented occurrences of a reaction, nor any statements to treaters that Petitioner experienced a vaccine reaction.[31] Testing results also do not support this conclusion. Respondent effectively rebutted Dr. Tornatore's arguments about the significance of eosinophil levels, establishing that (a) absolute eosinophil count matters more than the percentage level, (b) other testing that would reveal inflammation, like the ESR rate or CRP levels, was negative, and (c) eosinophilia is not otherwise deemed a marker of MS.

The record in this case is simply inconsistent with Petitioner's contention that he experienced a serious deterioration of his MS due to vaccination. It is not enough for him to argue that he literally became "worse" in the days immediately after receipt of the last HPV dose – for that is another way of simply invoking the temporal relationship between vaccine and injury, a relationship well understood in the Program to have little evidentiary bearing when determining entitlement. *See, e.g.*, *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014) ("[a] temporal correlation alone is not enough to demonstrate causation"). Even if the third HPV dose transiently provoked an initial worsening of his then-ongoing symptoms, the record does not establish that Petitioner's *subsequent* illness course was worse overall.

[31] The fact witness affidavits filed in support similarly do not contend that Petitioner (or his parents) expressed any concerns related to a vaccine-induced injury to a treater around the time of vaccination or thereafter. *See generally* Maciel First Aff.; Maciel Second Aff.

C. *Petitioner Has Not Established a Plausible Causation Theory*

My disposition of this case primarily turns on the factual findings above. However, having heard the experts and reviewed each side's medical literature, I also find that Petitioner has not *in this case* presented a plausible theory, supported by sufficient reliable evidence, that the HPV vaccine *could* exacerbate an existing course of MS.

The Petitioner did offer some reliable evidence in support of the "can cause" element of his claim. The scientific evidence filed in this case included some recommendations from reliable medical sources like the National MS Society that vaccines not be administered during the midst of an MS relapse. *See* Ex. 18; Tr. at 19, 21; *see also* Jefferey. Dr. Javed for his part seemed to acknowledge the reasonableness of this view. Tr. at 167. It could also be inferred from the medical record that Petitioner received the third HPV dose only because his initial symptoms were not understood by treaters to be MS (although it does not appear from the medical records that any of those symptoms were discussed or mentioned at the time Petitioner received the third HPV dose).

However, Petitioner was tasked with demonstrating, with reliable scientific or medical evidence, that the HPV vaccine can *worsen* an individual's subsequent overall course – not just that a vaccine might be deemed to pose a transient risk during a flare. To support this larger contention, Petitioner offered no literature discussing the concept directly, and Dr. Tornatore did not relate in his testimony particularized observations from his own medical experience that would render this contention plausible. Tr. at 57. Instead, he relied heavily on case reports involving different, more limited demyelinating conditions like NMO, or (at best) MS exacerbation after receipt of different vaccines like the Hep B.

Respondent, by contrast, offered reliable scientific epidemiologic evidence[32] directly relating to the HPV vaccine and MS, and suggesting the absence of a relationship. *See, e.g.*, Grimaldi-Bensouda; Miranda; Chao; Mailand. Although not all of this literature directly involves the propensity of the HPV vaccine to cause an exacerbation (as opposed to directly initiate an autoimmune process culminating in MS), its overall probative value outweighed the case reports (a type of evidence that in the Program is not typically given great weight) that Petitioner emphasized. *See, e.g., K.O. v. Sec'y of Health & Human Servs.*, No. 13-472V, 2016 WL 7634491, at *11-12 (Fed. Cl. Spec. Mstr. July 7, 2016) ("single case studies d[o] not contain any meaningful analysis of causation"); *Bast v. Sec'y of Health & Human Servs.*, No. 01-565V, 2012 WL 6858040, at *38 n.104 (Fed. Cl. Spec. Mstr. Dec. 20, 2012) ("[c]ase reports generally carry little weight on the issue of causation") (citing *Campbell v. Sec'y of Health & Human Servs.*, 90 Fed. Cl. 369 (2009)). At a minimum, there is not enough reliable and persuasive evidence offered herein for me

[32] The Federal Circuit has underscored the reasonableness of evaluating on-point epidemiologic evidence when weighing the success of a petitioner's showing in a Vaccine Act case. *See D'Toile v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811-12 (Fed. Cir. Apr. 12, 2018). To do so does not impose upon the petitioner the burden of *offering* such evidence to prevail.

to find it plausible that the HPV vaccine could significantly aggravate the overall course of MS - as opposed to simply make worse, for a limited time, an existing flare.

Dr. Tornatore otherwise could not imbue Petitioner's theory with the evidentiary weight missing from the individual items of filed literature. Overall I found him to be a competent and credible expert, with more than sufficient expertise on the topic of MS and interpretation of the radiologic evidence relevant to it to opine in this case. His general background means that his opinion that a vaccine could produce an MS flare given the innate immunologic properties of any vaccine is entitled to some consideration. However, Dr. Tornatore's professional focus is not on immunologic matters, and therefore his overall credibility and expertise on the topic of MS was not enough to imbue this sub-component of his testimony with the evidentiary heft needed to outweigh Respondent's more robust, literature-supported contentions that the HPV vaccine specifically is *unlikely* to contribute to the processes resulting in MS, cause a damaging flare, or worsen an existing flare to the degree necessary to significantly aggravate a course of MS.

My determination is consistent with other persuasive prior decisions (which are not controlling of the outcome herein but provide helpful guidance).[33] Such decisions support the conclusion as a general matter that cases of preexisting, symptomatic MS (as opposed to RIS-like instances in which the MS is not only undiagnosed but has not even presented clinically) are unlikely to be exacerbated merely by the stimulation of the innate immune system occasioned by receipt of a vaccine. *See, e.g., Bubb*, 2005 WL 1025707, at *20-21, 24. Future studies may well provide the evidentiary corroboration presently missing,[34] but the proposal that the HPV vaccine could aggravate MS's overall course has not *in this case* been established to be plausible.

CONCLUSION

Based upon the aforementioned analysis, I conclude that Mr. Maciel has not carried his burden of proof, and therefore I must DENY entitlement in this case.

[33] I also have recently had the occasion to consider whether the flu vaccine could exacerbate an existing course of MS. There, as here, I found that the medical and scientific evidence filed were insufficient to amount to a plausible causation theory. *See, e.g., Zuzow v. Sec'y of Health & Human Servs.,* No. 14-920V, slip. op. at 25-26 (Fed. Cl. Spec. Mstr. Aug. 24, 2018) (although reliable evidence supported a connection between the flu vaccine and the *initiation* of MS, substantial literature rebutted the contention that it could also worsen an existing case of MS).

[34] As in any Vaccine Program case, a different combination of evidence – additional studies (as opposed to case reports) regarding how the stimulation of the innate immune system inherent to vaccination can exacerbate MS or a comparable CNS demyelinating autoimmune disease, coupled with expert testimony from an individual with demonstrated experience studying the matter and/or a specific immunologic background – could move the needle toward the determination urged by Petitioner herein.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accord with this decision.[35]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[35] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.