CORRECTED

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 13-471V

Filed: June 30, 2023

Reissued for Public Availability: July 25, 2023

* * * * * * * * * * * * * *		
WENDY WILLIAMS,	*	
	*	
Petitioner,	*	
	*	Hepatitis A/B Vaccine;
	*	Optic Neuritis; Multiple Sclerosis;
SECRETARY OF HEALTH	*	Significant Aggravation
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	
	*	
* * * * * * * * * * * * * *		

Wendy Williams, Pro Se.
Benjamin Warder, Esq., U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On July 12, 2013, Wendy Williams ("Ms. Williams" or "petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*[2] (the "Vaccine Act" or "Program"). Petitioner alleges that she developed multiple sclerosis ("MS") after receiving a Twinrix ("hepatitis A/B") vaccination on February 16, 2011. *See* Petition ("Pet."), ECF No. 1; Amended Pet., ECF No. 159.

After a complete review of the record and for the reasons discussed in this Ruling, I find that petitioner has presented preponderant evidence that the hepatitis A/B vaccination petitioner

[1] Because this Ruling contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the internet.** However, the parties may object to the Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen 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 whole Ruling will be available to the public. *Id.* This Ruling originally issued on June 30, 2023 and the parties were afforded fourteen days to propose redactions. The parties did not propose any redactions. Accordingly, this Ruling is reissued in its original form for posting on the Court's website.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2018).

received significantly aggravated her previously asymptomatic multiple sclerosis.

I. Procedural History

This case has a prolonged and protracted procedural history. The petition was filed by Meredith Daniels of Conway, Homer, P.C. on July 12, 2013 and was initially assigned to Special Master Dorsey. ECF No. 1, 3. Medical records in the form of a compact disc were received by the Clerk's Office on July 26, 2013. An initial status conference was held on September 5, 2013. Petitioner was ordered to file all outstanding medical records and a statement of completion. ECF No. 10. Petitioner filed a status report on October 4, 2013, indicating that she had filed all records to date, apart from records from one facility that she was still trying to obtain. ECF No. 12. On November 4, 2013, petitioner filed the remaining outstanding record and an amended statement of completion. ECF Nos. 14-15, Pet. Ex. 14.

Respondent filed his Rule 4(c) Report on February 7, 2014, recommending against compensation. ECF No. 19. Another status conference was held on April 3, 2014, following which petitioner was ordered to file outstanding medical records and an expert report. ECF No. 21. Petitioner filed additional medical records on April 30, 2014, ECF No. 22, Pet. Ex. 15, and on June 4, 2014, ECF No. 26, Pet. Ex. 16-17. Her expert report was filed on August 15, 2014. ECF No. 31, Pet. Ex. 18-19. Petitioner filed a supplemental expert report on May 13, 2015. ECF No. 48, Pet. Ex. 22. On July 27, 2015, respondent filed his expert report. ECF No. 53, Resp. Ex. Q. The parties filed a joint status report on September 14, 2015, in which respondent maintained his position that the case was not appropriate for compensation. ECF No. 55.

This matter was reassigned to me on October 22, 2015. Notice of Reassignment, ECF No. 56-57. A status conference was held on November 13, 2015, and the parties were instructed to file a joint status report on the possibility of settlement. ECF No. 58. The parties filed a joint status report on December 14, 2015, advising that respondent was "willing to entertain a demand." ECF No. 59. The parties engaged in settlement discussions through October 2018.

On October 19, 2018, petitioner's then counsel moved for Interim Attorneys' Fees and Costs. ECF No. 95. On October 22, 2018, attorney Richard Gage was substituted as petitioner's attorney. ECF No. 96. Settlement negotiations continued but ultimately failed. ECF No. 98. On January 15, 2019, the undersigned awarded attorneys' fees and costs to petitioner's prior counsel. ECF No. 101.

The matter was referred to ADR on January 29, 2019. ECF No. 106. Additional documentation was filed thereafter in support of petitioner's damage claim. After almost a year in ADR, petitioner filed a status report advising that continuing with ADR would likely be unsuccessful. The matter was returned to the undersigned on January 2, 2020. ECF Nos. 110-111. Throughout 2020, both parties filed additional medical literature and expert reports. Petitioner filed updated medical records. A one-day hearing was held via video conference on February 18, 2021. Following the hearing, petitioner filed an amended petition. Amended Pet., ECF No. 159.

Respondent filed a post-hearing brief on August 20, 2021. ECF No. 166. Petitioner filed her post-hearing brief on August 23, 2021. ECF No. 167.

The parties were again encouraged to resume settlement discussions. They agreed. For the next 14 months it appeared as though the parties were actively engaged in settlement negotiations. However, on October 4, 2022, petitioner sent an email to chambers advising that she intended to proceed pro se. Several status conferences took place over the following months. ECF No. 174, 177-79. Petitioner's counsel was ordered to provide petitioner with all evidence for damages in his possession. ECF No. 179. On January 19, 2023, Mr. Gage filed a Motion to Withdraw as Attorney of Record. ECF No. 182. The Motion to Withdraw was granted on February 9, 2023, after confirming that Mr. Gage had provided petitioner with all the evidence on damages in his possession. ECF No. 185.

This matter is now ripe for ruling on entitlement.

II. Issues to be Determined

In a Joint Stipulation filed prior to the hearing the parties agreed to the following: Petitioner received Twinrix (hepatitis A/B) vaccinations on April 26, 2010 and February 16, 2011; On March 3, 2011, petitioner underwent brain magnetic resonance imaging ("MRI") which revealed numerous white matter lesions, several of which were enhancing with restrictive diffusion indicative of active demyelination; An MRI of the right eye showed enlargement of the optic nerve; On March 4, 2011, petitioner was diagnosed with optic neuritis; Petitioner was subsequently diagnosed with multiple sclerosis. Joint Pre-Hearing Submission, ECF No. 153. The parties agreed that petitioner had evidence of multiple brain lesions, typical of MS, prior to her February 16, 2011 Twinrix vaccination. *Id*. at 1-2.

However, during the hearing, Dr. Tornatore testified that non-enhancing lesions do not necessarily reflect old lesions but rather could be new lesions too small to enhance on MRI or lesions that were no longer enhancing at the time of the MRI. Tr. 59-60. Therefore, the hepatitis A/B vaccine could have either caused brain lesions to develop, leading to petitioner's MS, or significantly aggravated pre-existing lesions, resulting in symptomatic MS.

Thus, the issue is whether the February 16, 2011 hepatitis A/B vaccine caused or significantly aggravated petitioner's multiple sclerosis. Tr. 168-71.

III. Medical Terminology

Prior to discussing this case, it is necessary to first define the medical terms that will be used throughout this Ruling.

The optic nerve[3] is an extension of the brain and has myelin like the rest of the brain. Optic neuritis ("ON") is an inflammation of the optic nerve. Tr. 65. Known causes of optic neuritis

[3] The optic nerve is the second cranial nerve, the so-called nerve of sight, actually part of the central nervous system throughout its course, misnamed as a nerve because of its cordlike appearance; it consists chiefly of axons and central processes of cells of the ganglionic layer of the retina, which leave each orbit through the optic canal, joining with those of the opposite side to form the optic chiasm (the medial or nasal fibers of each nerve crossing over to the

include sarcoidosis, some viruses, MS (being the most common), granulomatous disease, and infection. Tr. 65.

Multiple Sclerosis is a chronic inflammatory demyelinating[4] disorder of the central nervous system ("CNS"). Resp. Ex. D at 1.[5] An estimated 2-2.5 million people worldwide suffer from MS, with twice as many women as men. The average age of onset is between 20 and 40 years old. *Id*. "MS is generally considered to be an autoimmune disease directed against CNS myelin or oligodendrocytes, with a multifactorial pathogenesis that appears to involve both genetic and environmental factors." *Id*. The suggestion that immune responses generated by infections and vaccinations may trigger or exacerbate CNS autoimmunity in susceptible individuals has made the implementation of universal hepatitis B vaccination controversial. *Id*.

A diagnostic hallmark of MS is the uptake of IV administered contrast material (gadolinium) in new lesions of the brain, signaling blood-brain-barrier ("BBB") breakdown and often reflects active perivascular inflammation in MS. Pet. Ex. 41 at 1, 4.[6] It has been demonstrated that lesion enhancement remains visible for one month on average. *Id*. at 1. In animal studies of Experimental Autoimmune Encephalomyelitis[7] ("EAE"), though not identical to MS but used as a model for studying the disease, enhancement has consistently lasted less than 5 days in acute EAE and less than 15 days in chronic EAE. *Id*.

In *Cotton et al*., MRIs of patients with relapsing-remitting MS ("RRMS") were studied weekly for 8 weeks, every other week for 16 weeks, then monthly in order to present a quantitative analysis of each new enhancing lesion that appeared during the first 6 weeks. Pet. Ex. 41 at 1; Resp. Ex. X.[8] Enhancements were followed until they were no longer seen on an MRI. The goal of the study was to better understand the natural history of RRMS for purposes of designing clinical drug trials. *Id*. The findings included: 1) the average duration of enhancement of MS lesions was lower than estimated and closer to what is observed in animal models for the disease (i.e. a duration of 1 or 2 weeks for new lesions, with new lesions demonstrating blood brain barrier breakdown for less than a week; 2) significant correlations were demonstrated between the duration of contrast enhancement and lesion volumes or growth rates; and 3) different lesions in the same patient appeared to develop largely independent of each other, demonstrating large variations in the duration of enhancement during the acute phase of evolution. *Id*. at 1, 4-5. The average duration of enhancement of new lesions was 3.14 weeks on average with the median being 2 weeks. *Id*. at 5. Fifty-five percent of new lesions were visible only on one or two weekly scans. *Id*. The volume of an enhancing lesion was dependent on the time between gadolinium injection and imaging, amount of gadolinium used, and age of the lesion. *Id*. Maximum enhancement was seen, on average, 29 minutes after the administration of IV gadolinium. *Id*. "Taken together, these findings

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opposite side), then continuing on each side as the optic tract. *Dorland's Illustrated Medical Dictionary* 1245, 1313. (33rd ed. 2019) [hereinafter "*Dorland's*"].

[4] Demyelination is destruction, removal, or loss of the myelin sheath of a nerve or nerves. *Dorland's* 480.

[5] V. Martínez-Sernández & A. Figueiras, *Central Nervous System Demyelinating Diseases and Recombinant Hepatitis B Vaccination: A Critical Systematic Review of Scientific Production*, 260 J. NEUROLOGY 1951 (2013), filed as "Resp. Ex. D."

[6] Francois Cotton, MD et al., MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals, 60(4) Neurology 640 (2003), filed as "Pet. Ex. 35", "Pet. Ex. 41", "Resp. Ex. C," and "Resp. Ex. X."

[7] Encephalomyelitis is inflammation involving both the brain and the spinal cord. *Dorland's* 607.

[8] Cotton et al., *supra* note 6.

may suggest that periods of heightened lesion activity lasting a few months (perhaps triggered by an exogenous event such as infection by a microorganism) alternate with periods of relative quiescence. Our results show that within such outbursts of lesion activity, however, considerable heterogenicity in the activity of individual lesion may exist. The complexities of individual lesion behavior remain largely to be explored." *Id*. at 6-7.[9]

IV. The Factual Record

a. Medical History

i. Prior to the Subject Hepatitis A/B Vaccine

Petitioner was born on December 2, 1975. She had no past medical history relevant to the injuries at issue. Pet. Ex. 2 at 20-26.

In 2008, at the age of 33, petitioner enlisted in the United States Army. Pet. Ex. 11 at 1. During her induction examination, a large fibroid tumor was found. Lupron, an anti-estrogen medication, was prescribed to shrink the tumor. Pet. Ex. 2 at 27; Pet. Ex. 1 at 15. However, petitioner was unable to tolerate the Lupron, so a myomectomy[10] was performed in April of 2009. Pet. Ex. 1 at 39. Petitioner had a normal June 2009 examination and was found to be neurologically intact, with normal strength and reflexes and no cranial or sensory deficits. *Id*. at 122, 130-31.

Due to her recent surgery, petitioner was placed in the Delayed Entry Program and presented for basic training on April 20, 2010. Pet. Ex. 8 at 1. On April 23, 2010, she received Tetanus-Diphtheria-Pertussis ("Tdap"), H1N1, meningococcal, and polio vaccinations. Pet. Ex. 7 at 1. On April 26, 2010, she received the first hepatitis A/B vaccination. *Id*.

Petitioner suffered from an upper respiratory infection and leg and ankle pain (fracture) treated with physical therapy in 2010. Pet. Ex. 2 at 200, 207, 222, 224.

She suffered from bacterial/allergic conjunctivitis in January of 2011, treated with medication. Pet. Ex. 2 at 155. On January 25, 2011, at her follow up appointment she was doing better, was compliant with medication, and had no history of recent upper respiratory infection ("URI"). *Id*. The assessment was resolved bacterial/allergic conjunctivitis. She was released without restrictions. *Id*. at 156.

ii. After the Subject Hepatitis A/B Vaccination

On February 16, 2011, petitioner was administered a second dose of Twinrix. Pet. Ex. 7 at 1. On February 23, 2011, petitioner presented to optometry and complained of distorted vision in her right eye for two days. Pet. Ex. 2 at 150-51. Examination revealed 20/35 vision on the right and normal vision on the left. *Id*. at 151. Dr. Beyersdorf was suspicious of right optic neuritis and scheduled petitioner for follow up and reevaluation in a week. *Id*. at 152.

[9] Cotton et al., *supra* note 6.
[10] A myomectomy is the surgical removal of a myoma, or fibroid tumor. *Dorland's* 1206.

Petitioner returned to optometry on March 3, 2011 with worsening vision. Examination of the right eye was now 20/40 with diminished red color vision and decreased pupil response. Pet. Ex. 2 at 142-44. Visit notes documented that petitioner saw fragments and distorted lines and had an abnormal anterior pupillary defect ("APD").[11] *Id*. at 143. MRIs for suspected optic neuritis were ordered. *Id*. at 144.

Petitioner had brain MRIs the same day, which revealed numerous abnormal white matter lesions with an appearance of distribution typical for demyelinating lesions[12] associated with MS. Several lesions were enhancing with restricted diffusion indicative of active demyelination. Pet. Ex. 2 at 1-2. An MRI of the right eye confirmed optic neuritis with diffuse enlargement and enhancement of the right optic nerve, consistent with manifestations of optic neuritis likely related to MS, given the presence of other brain lesions. *Id*. at 3.

The following day, March 4, 2011, petitioner was examined by ophthalmologist Dr. Smith who confirmed the MRI results were consistent with MS and ordered intravenous ("IV") steroids. Pet. Ex. 2 at 126. Petitioner received IV steroids in the hospital on March 4, 5, and 6, 2011. *Id*. at 13-16.

Petitioner underwent a lumbar puncture ("LP") on March 28, 2011. Pet. Ex. 2 at 37. On March 30, 2011, she presented to neurologist Dr. Halliday for visual problems and her LP results. Dr. Halliday diagnosed her with clinically isolated syndrome or "a first neurologic episode that lasts at least 24 hours, and is caused by inflammation/demyelination in one or more sites in the CNS . . . The episode can be monofocal or multifocal". *Id*. at 116-18. Dr. Halliday noted a high risk for developing MS due to the presence of lesions on the brain MRI. *Id*. at 118. He prescribed daily injections of Copaxone, a medication used to treat developing MS. *Id*.

On April 5, 2011, petitioner presented to Dr. Pham at the Army Family Practice Clinic for follow up. She reported continued blurry vision of the right eye and that she tired easily. She was training to be a lab technician. She had no family history of MS. Petitioner was released with work/duty limitations. Pet. Ex. 2 at 112-13.

Petitioner presented to Dr. Naalbandian, a neurologist at the Alexandria Neuro Center, on May 10, 2011. She reported slightly improved vision but major fatigue. Pet. Ex. 4 at 12-13. Dr. Naalbandian noted that petitioner had no history of prior attacks suggestive of transverse myelitis,[13] cerebellar dysfunction, sensory or motor abnormality. *Id*. at 13-14. Her neurological examination was normal. However, based on her recent history and MRI results, he believed petitioner likely had MS. *Id*. at 14-15. Dr. Naalbandian ordered an electroencephalogram

[11] Anterior pupillary defect is tested by shining a light into the eye. It is normal for the pupil to constrict. With optic neuritis, the pupil will dilate. Tr. 12.

[12] Demyelinating lesions are damaged areas in the brain and spinal cord caused by the immune-system attack. The exact type and severity of the symptoms that results depends on the number of lesions and the area of the central nervous system that's damaged. National Multiple Sclerosis Society, *Demyelination and Multiple Sclerosis*, https://www.nationalmssociety.org/What-is-MS/Definition-of-MS/Demyelination-and-Multiple-Sclerosis (last visited May 31, 2023).

[13] Transverse myelitis is inflammation of the spinal cord in which the functional effect of the lesions spans the width of the entire cord at a given level. *Dorland's* 1201.

("EEG")[14] which was conducted on May 31, 2011. *Id*. at 19. The assessment was an "essentially normal EEG." *Id*. Petitioner was instructed to continue taking Copaxone. *Id*. at 10-11.

At a follow up with Dr. Naalbandian on July 27, 2011, petitioner reported improved vision with occasional fatigue. She was to continue taking Copaxone and follow up with her eye doctor. Pet. Ex. 4 at 7-8. That evening, petitioner presented to the ER with nausea, dehydration, shortness of breath, and weakness. She was treated for an allergic reaction and was advised to contact her neurologist prior to taking any more Copaxone. Pet. Ex. 2 at 101-03. Petitioner reached out to Dr. Naalbandian who advised her not to take the Copaxone until she was re-evaluated. Pet. Ex. 4 at 9.

Petitioner presented to cardiologist Dr. Mathew on August 15, 2011 with complaints of numbness, tingling, dizziness, and irregular heartbeats. Pet. Ex. 3 at 9.

On August 23, 2011, petitioner presented to Dr. Halliday to begin proceedings for medical separation from the Army. Dr. Halliday documented right optic disc atrophy and a high risk of developing MS based on MRI findings. Pet. Ex. 2 at 87-88.

Petitioner presented to Dr. Ly at the Family Practice Clinic on September 1, 2011 to determine the need for a Medical Evaluation Board ("MEB") proceeding. Pet. Ex. 2 at 79. She complained of persistent blurry vision and stomach issues. She was diagnosed with irritable bowel syndrome and demyelinating disorder. *Id*. at 80-81.

Petitioner presented to her primary care physician ("PCP") Dr. Diroma on September 7, 2011 with joint pain in her elbows, shoulders, hips, knees, and ankles. She was diagnosed with arthralgia.[15] Pet. Ex. 2 at 76-78.

At her return visit with Dr. Naalbandian on September 19, 2011, she was not taking Copaxone but had no symptom changes. Her blurred vision continued. Dr. Naalbandian recommended evaluation at the Multiple Sclerosis Clinic at Louisiana State University ("LSU") Medical Center. Pet. Ex. 4 at 5-6. Petitioner requested information on Rebif.[16] She was to follow up in a month. *Id*. at 6. It was documented that she had a history of ON of the right eye and an abnormal MRI of the brain with enhancing white matter lesions most consistent with MS. *Id*. at 5.

A disability evaluation was conducted by Dr. Friedrich on September 23, 2011, following which she was determined to have failed retention standards. Specifically, she was unable to perform active duties in the military: soldier cannot make any type of maximum effort which leads to profile restrictions, cannot carry and fire assigned weapon, cannot evade direct and indirect fire which requires maximum effort, cannot ride military vehicle for 12 hours a day, cannot wear helmet 12 hours a day, cannot wear body armor or load bearing equipment 12 hours a day, cannot

[14] An electroencephalogram is a recording of the potentials on the skull generated by currents emanating spontaneously from nerve cells in the brain. The normal dominant frequency of these potentials is about 8 to 10 cycles per second and the amplitude about 10 to 100 microvolts. Fluctuations in potential are seen in the form of waves, which correlate well with different neurologic conditions and so are used as diagnostic criteria. *Dorland's* 594.

[15] Arthralgia is pain in a joint. *Dorland's* 154.

[16] Rebif is an anti-inflammatory medication to treat MS. *Rebif*, https://www.rebif.com/home html (last visited May 31, 2023).

carry 40 pounds, and cannot live in less sanitary conditions. Pet. Ex. 2 at 71. Dr. Friedrich documented that "[w]ith only a year in service when she first developed symptoms, it is certainly possible the disease began prior to service. However, there is no way to confirm this. Therefore, I believe it is prudent to conclude it developed after she began service." *Id*. at 72.

A repeat MRI of the brain performed on September 27, 2011, revealed an increase in the number of small white matter lesions in the periventricular and subcortical white matter of both cerebral hemispheres. Pet. Ex. 2 at 5. Several lesions were enhancing, indicative of active demyelination. *Id*. at 5-6. An MRI of the right optic nerve showed improvement in both degree of enlargement and enhancement when compared to the MRI of March 3, 2011. Very minimal asymmetrical enhancement was seen within the optic nerve. *Id*. at 7-8.

On September 29, 2011, Dr. Naalbandian again urged petitioner to go to the LSU MS Clinic after discussing her MRI results. Pet. Ex. 4 at 4.

At a visit with Dr. Diroma on September 30, 2011, petitioner complained of fatigue and depression. She was concerned about her diagnosis, her future, and the MEB proceeding. Pet. Ex. 2 at 64-65. Dr. Diroma referred her to the psychology clinic and prescribed Ambien so she could get some sleep. *Id*. at 66. Petitioner advised Dr. Diroma on October 5, 2011 that she was feeling better and ready to return to work. *Id*. at 60.

Petitioner presented to and was admitted to the MS Center at LSU on October 26, 2011 with malaise, fatigue, and abnormal gait. Pet. Ex. 5 at 2, 5. Dr. Minagar diagnosed her with an MS relapse and ordered five days of IV steroids. *Id*. at 6. Petitioner improved and was discharged on October 28, 2011 with a prescription for Rebif. *Id*. at 8.

Petitioner started Rebif and reported chills, aching, and fatigue. Pet. Ex. 5 at 75-76. She returned to Dr. Minagar on November 23, 2011 with complaints of weakness of her extremities, chronic fatigue, and gait ataxia. *Id*. at 76. Examination revealed ataxic gait and an inability to tandem walk. *Id*. at 76-77. The diagnosis was RRMS, paraparesis, and gait ataxia. *Id*. at 77.

That same day, Dr. Minagar provided petitioner with a request for a permanent exemption from the flu vaccine. Pet. Ex. 2 at 44. Dr. Nevin granted the exception on November 28, 2011, noting that while flu vaccination is not contraindicated in MS patients, recent flares or treatment for MS creates complications due to some evidence that flu and other vaccines have decreased efficacy after immune therapy. *Id*. at 43. Management and diagnosis of vaccine versus medication side effects pose challenges. For those reasons, the exemption was granted and was to remain in effect while petitioner was undergoing therapy for MS and likely through her separation from the military. *Id*. Petitioner worked as a greeter and information desk worker at that time and was cautioned about hand and respiratory hygiene and told to report if she had any symptoms of illness. *Id*.

Petitioner continued to complain of brief episodes of blurry vision. Her diagnosis remained stable optic neuritis and MS. Pet. Ex. 6 at 1.

Petitioner was hospitalized on February 13, 2012 with an MS flare involving worsening fatigue and generalized weakness. Pet. Ex. 5 at 95, 97. A February 14, 2012 brain MRI showed an enhancing lesion in the right temporal parietal region with "remarkable improvement" when compared to the September 2011 MRI. *Id*. at 123. She received 3 days of IV Solu-Medrol while in the hospital, which was tolerated well and mildly improved her weakness. *Id*. at 93-94. She was discharged and instructed to continue taking Rebif. *Id*. at 94. Dr. Minagar provided a written request for an exemption from early morning duties and strenuous physical activities due to extensive fatigue, weakness, and neurological deficits associated with RRMS. Pet. Ex. 9 at 32. It was recommended that petitioner's job be limited to desk duty, no heat or cold exposure, no climbing ladders or lifting objects greater than 10 pounds, and the ability to walk around periodically to relieve spasms and spasticity. Special accommodations were needed until discharge. *Id*.

Petitioner did well until May 7, 2012 when she developed stiffness and weakness in her neck and shoulders and thought she was having another MS relapse. Pet. Ex. 10 at 4-6. Her treatment plan included steroids and two weeks of complete bedrest. *Id*. at 6. She was also given a prescription for potassium chloride and Pepcid. *Id*. By June 2012, she was stable. *Id*. at 18.

Petitioner was formally released from duty on August 17, 2012 due to "physical disability" effective October 27, 2012. The discharge noted Dr. Friedrich's assessment that petitioner was unable to perform her military job as a lab technician due to increased fatigability, high risk exposure, and the requirement for hepatitis vaccines. *See generally* Pet. Ex. 8. She qualified for Medicare in February 2014. Pet. Ex. 21 at 5.

Petitioner continues to suffer from relapsing remitting MS, requiring daily medication. *See generally* Pet. Ex. 20; Pet. Ex. 33. Updated medical records reflect right sided sensory disturbance, balance and motor issues, and MRIs with enhanced lesions. Pet. Ex. 33 at 108-09, 132. In December 2019, there were demyelinating lesions of the spine at C3-4 with multilevel degenerative changes, severe spinal canal stenosis, and cord compression at C5-6 and C6-7. Pet. Ex. 32 at 5. A brain MRI showed a significant increase in the number of demyelinating lesions since 2013. She continued to have enhanced lesions compatible with active demyelination. *Id*. She continues to suffer from chronic fatigue with pins, needles, and numbness to the right side of her body. She also struggles with major depressive disorder secondary to chronic illness, is disabled, and isolates at home due to pain and fatigue. *See generally* Pet. Ex. 20; Pet. Ex. 23; Pet. Ex. 25.

b. Affidavits of Petitioner

Petitioner submitted two affidavits. Although present at the hearing, petitioner did not testify.

Petitioner affirmed that she was in excellent health other than common illnesses prior to her receipt of the subject vaccine. She underwent surgery for a fibroid tumor at age 33. Pet. Ex. 11 at 1. Petitioner did not undergo any CT scans or MRIs prior to March 3, 2011. Pet. Ex. 13.

According to petitioner, after looking for work unsuccessfully for years, she decided to join the Army and started the process in 2008. Pet. Ex. 11 at 1. During the initial entry process, it was

discovered she had fibroid tumors. Following surgery in April of 2009, she was ineligible to enlist for six months to allow for proper healing before basic training. *Id*. She then had to wait an additional 6 months due to the amount of people joining the Army at that time. *Id*. at 2.

Petitioner affirmed that upon arriving at basic training on April 20, 2010, she received a "multitude of vaccinations", including Twinrix and a flu vaccine on April 26, 2010. Pet. Ex. 11 at 2. In the weeks following her vaccinations, she was "excessively tired" which she attributed to the nature of basic training. However, the fatigue never went away even later when she was in less physically demanding environments. *Id*.

Petitioner affirmed receipt of a second dose of the Twinrix vaccine on February 16, 2011. Five days later while driving on a sunny day, the vision in her right eye became distorted. Pet. Ex. 11 at 2. She thought there was fog on the windshield and tried to wipe it away, but it was still there. When she went to optometry the next morning, she was informed that they did not take walk in patients, so she scheduled an appointment for February 23, 2011. *Id*. Following examination, she was told that there was nothing wrong. She insisted that she could not see out of her right eye. She was told to return in a week. *Id*.

Petitioner affirmed that she returned on March 3, 2011 and testing showed that her right pupil did not react. Pet. Ex. 11 at 3. MRIs were performed that day and she was diagnosed with right optic neuritis along with multiple enhancing lesions on her brain. *Id*. She was admitted to the hospital the next day for IV steroids and subsequently treated with "disease modifying therapy, including injections of Copaxone". *Id*.

Petitioner affirmed ongoing decline in her abilities, including episodes of limited vision that affect all tasks requiring good visibility and hand eye coordination. Pet. Ex. 11 at 3. When these episodes occur, she cannot drive or work on the computer for a long time. She has chronic, unrelenting fatigue. *Id*. She is immunocompromised and suffers constant infections. Her medications include immunosuppressants and interferons which cause flu like symptoms. *Id*.

According to petitioner, although her vision improved and despite continuous treatment, her September 2011 MRI showed new lesions. Pet. Ex. 11 at 4. Her condition has resulted in deepening depression, difficulties with concentration and interacting with others, greater fatigue, and stress. Insufficient rest or sleep incite a relapse of her MS. *Id*. at 4-5.

Petitioner dreamed of having children, but the MS medications preclude that. Adoption is not an option due to her MS and uncertainty of whether she will be able to take care of herself. Pet. Ex. 11 at 4.

Petitioner affirmed her love of the outdoors and being active and social. Pet. Ex. 11 at 5. She is now depressed, fatigued, and in constant pain and her life is dictated to by a medication schedule. *Id*. Before her vaccine, she was an "Active duty soldier." She was then sent to the Army Medical Examination Board, which is standard operating procedure for conditions like MS and optic neuritis, and she was found to have failed to meet retention standards because of her condition. *Id*. According to petitioner, she "was set to become an officer" but lost her career in

basic training due to the vaccinations and was medically discharged in October of 2012. *Id*. She is disabled, which also precludes her from working in the civilian sector. *Id*.

V. The Experts' Opinions

a. Petitioner's Expert, Dr. Carlo Tornatore

i. Qualifications

Dr. Tornatore has an undergraduate degree in neurobiology from Cornell University, an M.S. from Georgetown University, Department of Physiology, and an M.D. from Georgetown University School of Medicine. Pet. Ex. 46 at 1-2. Dr. Tornatore is the Chairman and Neurologist-in-Chief, Department of Neurology, for Medstar Georgetown University Hospital; Chairman, Department of Neurology for Georgetown University Medical Center; Regional Director for Neurology, Medstar Health; and Professor of Neurology at Georgetown University Medical Center. *Id*. at 2-3. He is also the Director of the Multiple Sclerosis Clinic at Georgetown University Hospital. *Id*. at 3. He is Board Certified in Neurology. *Id*. at 1.

Dr. Tornatore has done "basic science work, translational work and clinical trial work in neuroimmunology and multiple sclerosis." His research on MS has been published. Tr. 5.

Dr. Tornatore authored two reports and testified at hearing. Pet. Ex. 18; Pet. Ex. 22.

ii. Expert Reports

Dr. Tornatore opined that the hepatitis A/B vaccination petitioner received on February 16, 2011 caused her optic neuritis and subsequent development of MS or triggered her pre-existing asymptomatic MS.

1. Prong I

In Dr. Tornatore's opinion, he has provided a scientifically sound and reliable theory for how the hepatitis A/B vaccination can result in the development or aggravation of MS.

He pointed to the Institute of Medicine ("IOM") which addressed the hepatitis B vaccine and its relationship with demyelinating neurological disorders through the mechanisms of molecular mimicry, bystander activation, and superantigen stimulation that could lead to central and peripheral demyelinating disease in response to vaccination. Pet. Ex. 18 at 15; Pet. Ex. 22 at 3; Pet. Ex. 42.[17] Dr. Tornatore explained that molecular mimicry is a process by which microbial antigenic determinant cross reacts with a self-protein. If the self-protein is a myelin related protein, the subsequent immunological response leads to autoimmune demyelination. Pet. Ex. 18 at 15; Pet. Ex. 22 at 3. Bystander activation is a process by which microbial infection or other stimulus

[17] Institute of Medicine, *Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders*, Nat'l Academic Press (2002) [hereinafter "Institute of Medicine 2002"], filed as "Pet. Ex. 36" and "Pet. Ex. 42."

leads to the release of large quantities of normally sequestered host proteins causing subsequent destruction of host tissue, which could include central or peripheral myelin. *Id*. Superantigens are proteins that are produced by viruses and bacteria and can activate T or B cells independent of antigen specificity of the responding lymphocytes and in so doing allow for activation of lymphocytes that are autoreactive. *Id*. Through these processes, it is conceivable that vaccines can trigger the same potentially damaging mechanisms. "Thus, there is a theoretical basis for a hepatitis B vaccine-induced immune response that could possibly lead to demyelination." *Id*.

Dr. Tornatore submitted that the IOM recognized a biological basis for how hepatitis B vaccine could lead to demyelination, although the evidence was "scant and indirect." Pet. Ex. 18 at 15-16; Pet. Ex. 42.[18] Previously, evidence of whether molecular mimicry existed between the hepatitis B vaccine proteins and the proteins within the central nervous system—which play a role in the pathogenesis of MS—was inconclusive. Studies did not find homology between the amino acid sequences of the main component of the hepatitis B vaccine ("HBsAg"), and the proteins—myelin oligodendrocyte glocoprotein ("MOG"), myelin basic protein ("MBP") and proteolipid protein ("PLP")—present on the nerves, thus making it unlikely that T cell mediated immune response against CNS autoantigens could trigger autoimmunity. *Id*. However, Dr. Tornatore submitted that then *Fujinami* & *Oldstone* observed that rabbits immunized with the hepatitis B polymerase peptide shared six amino acids with MBP and developed an antibody response to MBP; in some cases, the rabbits developed CNS lesions reminiscent of EAE. Pet. Ex. 44 at 3.[19]

Thereafter, and building on the findings by *Fujinami* & *Oldstone*, the authors in *Gran et al. I* studied the hepatitis B polymerase and its capacity to cross-react with myelin antigens. Pet. Ex. 22 at 5; Pet. Ex. 44 at 1.[20] *Gran et al. I* concluded that there may be a need for several events to occur simultaneously for "physiological cross-recognition" to become "dangerous mimicry" and "frank autoimmunity", which is why autoimmune diseases are so rare. Pet. Ex. 44 at 7. Further, unlike other organs, "the CNS may be protected from immune mediated damage by the high selectivity of the BBB [blood brain barrier] and the very low expression of MHC molecules." *Id*. They concluded that molecular mimicry remains a valid hypothesis for autoimmunity; however, "the requirements for cross-reactivity are more flexible than previously appreciated." *Id*.

Dr. Tornatore submitted that the authors in *Gran et al. I* determined that sequence homology was not necessary for molecular mimicry to occur. They found that "[b]oth clinical and experimental evidence supports the hypothesis that immune mechanisms are involved in the pathogenesis of inflammatory demyelination in multiple sclerosis (MS) and that autoreactive T lymphocytes initiate the process of central nervous system myelin damage". Pet. Ex. 18 at 16; Pet. Ex. 22 at 5; Pet. Ex. 44 at 1.[21] The authors noted that in recent studies on mechanisms associated with T-cell activation, at least for some T-cell clones, antigen recognition was shown to be much more "degenerate" than previously thought and sequence homology was not necessary for cross-activity. Pet. Ex. 44 at 1. The authors explained that EAE, which resembles MS, is induced in

[18] *Id*.
[19] The original *Fujinami* & *Oldstone* article appears to have not been filed in this matter.
[20] Bruno Gran, MD, et al., *Molecular Mimicry and Multiple Sclerosis: Degenerate T-Cell Recognition and the Induction of Autoimmunity*, 45 ANN. NEUROLOGY 559 (1999), filed as "Pet. Ex. 38" and "Pet. Ex. 44." The 1999 Gran et al. article will be referred to as "*Gran et al. I*".
[21] *Id*.

animal studies by CD4+ T cells and serves as the basis for research into the role of CD4+ T cells in MS. *Id*. at 2. More specifically, EAE is induced in susceptible animals by immunizing them with myelin antigens such as MBP or proteolipid protein or peptides derived from antigens. *Id*. The EAE model provides the pathogenic steps that may be relevant to MS, "including (1) genetic susceptibility, (2) priming and activation of myelin-specific T cells, (3) interaction of autoreactive T cells with endothelium and migration into the CNS, and (4) recognition of myelin antigens and initiation of inflammatory or demyelinating damage." *Id*.

Autoreactive T cells are part of the immune repertoire of heathy, nonimmunized animals, and the role of genetics may play an important role in disease susceptibility and the function and frequency of T cells. Pet. Ex. 44 at 2.[22] "For potential autoreactivity to become overt autoimmunity, however, myelin-reactive T cells must be activated by immunization with myelin antigens or strong unspecific stimuli such as bacterial superantigens." *Id*. Molecular mimicry is the notion that "cross reactive foreign antigens can activate autoimmune T cells, and subsequently mediate pathological and clinical damage. Once activated in the periphery, autoreactive T cells can cross the blood-brain barrier (BBB), infiltrate the CNS, recognize myelin antigens, and damage oligodendrocytes and the myelin sheath by various effector mechanisms." *Id*.

Finally, the authors concluded that "[b]ased on epidemiological data linking viral infections to MS exacerbations and possibly to the cause of the disease, viral antigens are attractive candidates for initiating autoimmune mechanisms through molecular mimicry." Pet. Ex. 44 at 2.[23] Thus, the molecular mimicry hypothesis provides the conceptual framework for how autoimmunity may be triggered. *Id*.

Dr. Tornatore further relied on *Bogdanos et al*., whose focus was on the hepatitis B vaccination's potential for immunological cross-reactivity in comparison to the safety and efficacy of the vaccine. Pet. Ex. 45 at 6.[24] The hepatitis B vaccine used in the study contained SHBsAg, not the HBsAg contained in the subject vaccine. *See id*.; Pet. Ex. 22 at 4. However, the authors concluded that, "not only does SHBsAg share strong homologies with major myelin antigens such as MBP and MOG but also specific viral/self-pairs were found to be targets of antibody responses induced by the administration of the viral vaccine." Pet. Ex. 45 at 6. By showing cross reactivity and the possible role of the hepatitis B vaccine as a trigger for molecular mimicry, the authors concluded further investigation was necessary. *Id*. at 7.

Finally, Dr. Tornatore offered *Gran et al. II* to demonstrate the link between the hepatitis B vaccine and MS. Pet. Ex. 18 at 16; Pet. Ex. 43.[25] The authors described a patient who had an "onset of clinically definite MS [three months] after hepatitis B vaccination". Pet. Ex. 18 at 16. The patient had hepatitis B surface antigen-specific CD4+ T cell clones present in his CSF and peripheral blood. These findings suggested that molecular mimicry occurred and resulted in the

[22] *Id*.
[23] *Id*.
[24] Demitrios-Petrou Bogdanos et al., *A Study of Molecular Mimicry and Immunological Cross-Reactivity Between Hepatitis B Surface Antigen and Myelin Mimics*, 12 CLINICAL & DEVELOPMENTAL IMMUNOLOGY 217 (2005), filed as "Pet. Ex. 39" and "Pet. Ex. 45."
[25] Bruno Gran et al., *Development of Multiple Sclerosis After Hepatitis B Vaccination: An Immunologic Case Report*, 54 NEUROLOGY A164 (2000), filed as "Pet. Ex. 37" and "Pet. Ex. 43." Since there are two articles by Gran et al. filed in this matter, the 2000 article will be referred to as "*Gran et al. II*".

patient's MS. The authors recommended further investigation into a possible trigger of autoimmune demyelination after hepatitis B vaccination. *Id*.; Pet. Ex. 22 at 5; *see also* Pet. Ex. 43.

In sum, Dr. Tornatore opined that the foregoing studies demonstrate that molecular mimicry is a persuasive explanation for the onset of demyelinating diseases like MS. Specifically, molecular mimicry between the hepatitis B vaccine antigen and myelin protein has been demonstrated. Pet. Ex. 43.[26] The hepatitis B surface antigen shares strong homologies with major myelin antigens, such MBP and MOG, and also shows that specific viral/self-pairs are targets of antibody responses induced by vaccine administration. Pet. Ex. 45.[27] On rare occasions, this process may result in demyelinating diseases. Pet. Ex. 18 at 16. Finally, there is evidence that exact sequence homology is not necessary for cross-reactivity to occur. Pet. Ex. 44.[28]

2. Prongs II and III

In Dr. Tornatore's opinion, there is a logical sequence of cause and effect between the vaccination and petitioner's ON and MS. Vaccines are designed to stimulate the immune system, but they may result in an aberrant immune response, which is what occurred here. Pet. Ex. 22 at 4, 5.

After detailing petitioner's medical history, Dr. Tornatore summarized the pertinent facts: On February 16, 2011, petitioner received a second Twinrix vaccination; On February 23, 2011, petitioner was evaluated for visual changes in the right eye of two-day duration; On March 3, 2011, MRI of the right eye with gadolinium revealed acute demyelination of the right optic nerve as well as acute demyelination in the hemispheres of the brain; On March 4, 2011, petitioner was diagnosed with optic neuritis; On March 28, 2011, her cerebrospinal fluid was normal; Petitioner was started on Copaxone for a presumptive diagnosis of MS. Pet. Ex. 18 at 14.

Dr. Tornatore submitted that the lesions observed on the March 3, 2011 MRI likely developed within a 2 week period prior to the MRI, "precisely the time [petitioner] had her HepA-HepB vaccination". Pet. Ex. 18 at 15, 16; *see also* Pet. Ex. 41.[29] Thus, he opined that the vaccine caused petitioner's lesions and subsequent MS. Alternatively, Dr. Tornatore argued that the subject vaccine significantly aggravated petitioner's pre-existing MS, given the presence of non-enhancing asymptomatic lesions seen on the MRI. Pet. Ex. 18 at 16-17; Pet. Ex. 22 at 5. The fact that the March 3, 2011 brain MRI showed non-enhancing lesions "suggest[ed] that there may have been asymptomatic antecedent inflammation that preceded the vaccination which was significantly aggravated by the hepatitis vaccination." *Id*. at 15. Dr. Tornatore opined that petitioner met the 2010 McDonald criteria for a diagnosis of MS based on her scans and clinical presentation. *Id*. With no prior symptoms, Dr. Tornatore posited that optic neuritis was petitioner's "MS-defining" event. *Id*.

Dr. Tornatore added that the enhancement of the right optic nerve seen on the March 3, 2011 MRI was acute. Pet. Ex. 22 at 4. He relied on *Cotton et al.* to show that the average duration

[26] *Id*.
[27] Bogdanos et al., *supra* note 24.
[28] Gran, MD, et al., *supra* note 20.
[29] Cotton et al., *supra* note 6.

of gadolinium enhancement of new lesions in 26 patients with RRMS was 3.07 weeks, with 2 weeks being the median. *Id*. at 4-5; *see also* Pet. Ex. 41 at 1, 4.[30] Therefore, in this case, the trigger for inflammation of the optic nerve most likely occurred two weeks prior to the MRI, which was around the time petitioner received the subject vaccination, resulting in "a striking sequence of cause and effect." Pet. Ex. 22 at 5; Pet. Ex. 18 at 15; Pet. Ex. 41 at 1. Dr. Tornatore added that the other enhancing lesions seen could be attributed to the vaccination for the same reason. Pet. Ex. 18 at 15; Pet. Ex. 22 at 5.

Dr. Tornatore added that the absence of oligoclonal bands in petitioner's March 28, 2011 lumbar puncture further indicated the acute nature of the inflammation seen on the MRI. Pet. Ex. 18 at 15; Pet. Ex. 22 at 5. Oligoclonal bands are produced by B cells and take up residence in the central nervous system; they are found in 95% of all MS patients. The absence of oligoclonal bands suggests that B cell stimulation or "trafficking" into the nervous system was relatively "nascent" or new. *Id*.

Dr. Tornatore added that because the February 16, 2011 hepatitis A/B vaccine was the second hepatitis A/B vaccination petitioner received, a brisk immune response was expected due to prior priming. Pet. Ex. 18 at 15.

In conclusion, Dr. Tornatore opined that, assuming petitioner had pre-existing lesions on her brain, the lesions were enhanced by the subject hepatitis A/B vaccine, constituting a significant aggravation under *Loving*. Pet. Ex. 22 at 5.

iii. Testimony

At hearing, Dr. Tornatore explained that the optic nerve is an extension of the brain with myelin like the rest of the brain. Optic neuritis is an inflammation of the optic nerve. A known cause of optic neuritis is multiple sclerosis. Tr. 65. He defined Relapsing Remitting Multiple Sclerosis as random episodic attacks of MS caused by inflammation with no known cause for the relapses. Tr. 83-84. "Somebody's immune system kicks up and causes inflammation". Tr. 84. He acknowledged that most patients with RRMS do not have an antecedent event that doctors can point to as the cause or trigger of their symptoms. Tr. 85.

The McDonald criteria used for diagnosing MS previously required two attacks. Tr. 50; Pet. Ex. 40.[31] The first attack included MRI findings for dissemination in time and space, meaning multiple events occurring at different times and at different sites of the central nervous system. If there is no dissemination in time or space, it could be an isolated incident. Tr. 51. The criteria used currently is less stringent, allowing for earlier treatment even where there is no enhancement on an MRI but where the CSF shows oligoclonal bands, which are evidence of dissemination in time. Tr. 51-52. Here, petitioner was treated with immunomodulatory agents after one attack which was appropriate. Tr. 52.

[30] *Id.*

[31] Chris H. Polman, MD, PhD, et al., *Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria*, 69 ANN. NEUROLOGY 292 (2011), filed as "Pet. Ex. 34" and "Pet. Ex. 40."

Dr. Tornatore stated that vaccines are meant to activate the immune system, so when there is a rare event after a vaccine such as a relapse in MS symptoms within the appropriate timeframe, it cannot be ignored. Tr. 84-85.

1. Prong I

Dr. Tornatore testified about the significance of the IOM findings. After discussing the biological mechanisms of molecular mimicry, bystander activation, and nonspecific or polyclonal T cell activation, the IOM committee concluded that "[i]f self-reactive T cells are activated by a nonspecific immune response, they could induce autoimmunity." Tr. 37; Pet Ex. 36 at 5; Pet. Ex. 42.[32] Further, the IOM stated that "[t]here is no reason in theory why hepatitis B surface antigen in the vaccine could not function in this way. Thus, there is a theoretical basis for a hepatitis B vaccine-induced immune response that could possibly lead to demyelination." Tr. 38; Pet. Ex. 42 at 7. He acknowledged that the IOM committee found the evidence "scant and indirect" but noted "we're dealing with a rare event here" that when coupled with the literature he submitted, provides the mechanism of how the hepatitis B vaccine could induce autoimmunity and speaks to the fact that it is scientifically demonstrated. Tr. 38.

Dr. Tornatore referenced *Gran et al. II*, authored by those well known in the MS community and presented at the Multiple Sclerosis Infection and Immunity Section of the American Academy of Neurology meeting. Tr. 38-39; Pet. Ex. 43.[33] Dr. Tornatore explained that *Gran et al. II* was a case study of a patient who developed MS three months after receiving a hepatitis B vaccination. Acknowledging that it was only one patient, Dr. Tornatore pointed out that the case study demonstrated active CD4 and CD8 T cell clones in both the patient's blood and CSF. Tr. 39-40. The authors "found cross-recognition of hepatitis B surface antigen and a proteolipid protein derived peptide by a T cell clone isolated from peripheral blood of a patient who developed MS after vaccination." Tr. 40-41; *see also* Pet. Ex. 43.[34] Thus, the authors concluded that molecular mimicry warrants further investigation as a possible trigger of autoimmune demyelination after hepatitis B vaccination. This study, like the IOM report, speaks to a link between the theory and reality of vaccine-related MS. Tr. 41.

Dr. Tornatore presented *Gran et al. I* published one year earlier than the above case study, which proposed the molecular mimicry hypothesis and postulated that myelin reactive T cell clones were activated by foreign antigens. Tr. 41-42; Pet. Ex. 44 at 1.[35] They showed that T cell clones can be activated by foreign antigens and react to myelin in both healthy patients and MS patients. Tr. 42. While it was previously thought that sequence homology between self and foreign antigens was necessary for cross recognition to occur, these studies showed that T cell receptors recognized a level of homogeneity that was not identical to the target antigen they were directed

[32] Institute of Medicine 2002, *supra* note 17.
[33] Gran et al., *supra* note 25.
[34] *Id*.
[35] Gran, MD, et al., *supra* note 20.

against. In other words, homology between antigens need not be exact.[36] Tr. 42-43; Pet. Ex. 44 at 1.[37]

Dr. Tornatore relied on *Bogdanos et al*. to build on his opinion that molecular mimicry and cross reactivity can occur between hepatitis B surface antigens and myelin mimics. Tr. 43-44; Pet. Ex. 45.[38] In the *Bogdanos et al*. study, the authors showed that the antibodies produced after vaccination reacted not only to the hepatitis B surface antigen, but also cross reacted with the myelin associated glycoprotein or myelin basic protein, even in patients who did not develop MS. Tr. 44, 89-90. Dr. Tornatore conceded that the fact that the authors demonstrated cross-reactivity did not necessarily establish that the vaccine caused a demyelinating disease. He explained that the development of a demyelinating disease such as MS would require a "rare potential confluence of things that happen". But the fact that it was not seen in the study did not mean it could not happen with the "right confluence of issues." Tr. 90. Like *Gran et al. II*, the authors in *Bogdanos et al*. determined that "the [hepatitis B] vaccine's possible role as an immunomodulator of viral/self cross-reactivity must be further investigated." Tr. 45; Pet. Ex. 45 at 1.[39]

Dr. Tornatore noted that two different investigators were able to show cellular and humoral response to the hepatitis B vaccine and "that's pretty good." Tr. 77. Dr. Tornatore added that these are rare events—the one in a million cases. Being unable to find a second patient does not mean it did not happen in the first. Tr. 78-79. The *Gran et al. II* paper showed that molecular mimicry following hepatitis B vaccination triggering MS was possible. Tr. 79. Then, the authors in *Bogdanos et al.* analyzed a larger group and demonstrated the link, even though the patients did not develop MS. Tr. 80. Dr. Tornatore submitted that a level of specificity beyond that will not be demonstrated because this is a rare event. Tr. 80.

Dr. Tornatore conceded that there is no literature that specifically says hepatitis B infection can cause optic neuritis. "We're talking about the indirect effect of an infection [through a vaccine] and then a subsequent molecular mimicry." Tr. 65. He submitted that epidemiological data will never show rare events; however, epidemiology will also not rule it out. It is so rare that no accumulation of cases exist for certainty—rather it is a concept. Tr. 66. The problem is trying to use statistical tools against rare events, "that's why we use these other prongs to try to understand…we're not going to have epidemiologic data, but [are] there other smoking guns or footprints or something that we can point to." Tr. 66-67. What makes this case so interesting to Dr. Tornatore is that there is a trigger to point to. Tr. 67.

On rebuttal, Dr. Tornatore revisited the *Bogdanos et al.* article, stating that the study did not use hepatitis B polymerase as stated by Dr. Sriram. Tr. 157-59; Pet. Ex. 45 at 1.[40] He explained that the authors examined "reactivity to at least one of the surface hepatitis B antigens, small hepatitis B surface antigen peptides—so not polymerase, but surface antigen—the same thing that's found in the vaccine was found in eight pre-hepatitis B vaccine subjects and those remaining

[36] Dr. Tornatore added that this concept is presently relevant and seen with the COVID vaccine. He explained that people are being vaccinated with a specific protein but still developing immunity to future variants with a different epitope. He testified that the T cell receptors have enough degeneracy that they will recognize the variants. Tr. 43.
[37] Gran, MD, et al., *supra* note 20.
[38] Bogdanos et al., *supra* note 24.
[39] *Id*.
[40] *Id*.

50 reacted to at least one of the peptides that appeared in 94 percent after vaccination". Tr. 158-59. The authors then analyzed MOG mimics to see whether there was hepatitis B cross reactivity against the surface antigen—again, not the polymerase. Tr. 159. Dr. Tornatore explained that "this paper clearly draws a straight line between hepatitis B surface antigen, not the polymerase, and I think MOG protein and other myelin proteins." Tr. 159. Dr. Tornatore agreed that the *Fujinami & Oldstone* study used hepatitis B polymerase on rabbits and found demyelination in the brain; though relevant, Dr. Tornatore posited that was not what is being discussed in this case. Tr. 159.

2. Prong II

According to Dr. Tornatore, although RRMS has no expected course, the tempo in this case was rapid and unlike anything he has seen in his own patients. Tr. 87. He opined that the vaccine was the triggering event that either caused or significantly aggravated petitioner's MS. Tr. 36, 59, 68, 87.

On January 25, 2011, prior to the February 16, 2011 hepatitis A/B vaccination, petitioner had a normal examination with no neurologic symptoms noted. Tr. 6; Pet. Ex. 2 at 155. Her visual acuity was 20/20 in both eyes following conjunctivitis. Tr. 7; Pet. Ex. 2 at 155. She had a negative APD. Tr. 7; Pet. Ex. 2 at 157.

On February 23, 2011, a week after the hepatitis A/B vaccination, petitioner presented to optometry and reported the onset of blurry vision two days before, or five days after the vaccination. She had no recent colds, infections, eye pain on movement, headaches, or light flashes. Tr. 10-11; Pet. Ex. 2 at 150-52. Her visual acuity was now 20/35. Tr. 11-12; Pet. Ex. 2 at 151. Her visual field was distorted when shown the Amsler grid,[41] which Dr. Tornatore described as a sign of visual disturbance of either the retinal or optic nerve. Tr. 12; Pet. Ex. 2 at 151. APD testing was normal. Tr. 12; Pet. Ex. 2 at 151. Dr. Tornatore explained that typically with ON, APD testing causes the pupil to dilate. Tr. 12. The fact that her APD testing was normal "speaks to something that is acute, a new onset, which goes along with her history." Tr. 14. A reason for her vision problems was not determined at this visit, but petitioner was educated on optic neuritis. Tr. 15.

When petitioner returned to the optometrist on March 3, 2011, her vision was now 20/40 and APD testing was abnormal with papillary defect. Tr. 16; Pet. Ex. 2 at 142-44. Petitioner had red cap desaturation, which is suggestive of ON, decreased color vision, and decreased light intensity in the right eye. Tr. 17; Pet. Ex. 2 at 144. The assessment was suspected posterior optic neuritis in the right eye. Tr. 17; Pet. Ex. 2 at 144. The optometrist ordered MRIs to be done the same day. Tr. 17-18; Pet. Ex. 2 at 144.

The next day, petitioner presented to the ER with worsening vision. Petitioner was administered IV Solu-Medrol, which Dr. Tornatore testified was consistent with the standard of care for ON. Tr. 19; Pet. Ex. 2 at 14-15.

[41] The Amsler grid is a set of charts showing various geometric patterns in black and white, e.g., grids or parallel lines, used for detecting defects of the central visual field. *Dorland's* 68, 333.

A lumbar puncture performed on March 30, 2011 showed only one nucleated white cell. Tr. 20; Pet. Ex. 2 at 11. Dr. Tornatore explained the significance of this result, stating that MS patients typically have upwards of 40 white blood cells. The presence of only one white blood cell further suggests the acute nature of the inflammation. Tr. 20-21. There were no oligoclonal bands—also known as IgG antibodies—found in the CSF, which was significant because he would have expected to see oligoclonal bands in the CSF if inflammation had been present for a longer time period. Tr. 21-23; Pet. Ex. 2 at 12.

Dr. Tornatore posited that the first clinical manifestation of petitioner's MS was her ON. Tr. 57. Had she been having demyelinating episodes before this point, Dr. Tornatore would have expected to see more symptoms. Tr. 59-60.

Dr. Tornatore also discussed the results of March 3, 2011 MRIs of the brain and right eye. Tr. 8; Pet. Ex. 2 at 1. The MRI of the brain showed numerous abnormal white matter regions with the distribution of typical demyelinating enhancing and non-enhancing lesions associated with MS. Tr. 8-9; Pet. Ex. 2 at 1-2. The MRI of the optic nerve showed diffuse enlargement and enhancement of the right optic nerve consistent with acute optic neuritis. Tr. 17-19; Pet. Ex. 2 at 3. These findings can be interpreted in two ways: 1) either the non-enhancing lesions were older than three weeks or 2) they were new lesions, but the inflammation was so minimal that there was no ability for the dye to cross the BBB. If the former were true, the question then becomes how old were the lesions exactly? Dr. Tornatore submitted that there is no way to know. Tr. 9, 59. Dr. Tornatore also pointed out that there were no black holes[42] seen on the March 3, 2011 MRI. Tr. 159-60.

Dr. Tornatore relied on *Cotton et al.* to support his opinion that the large lesions were less than two to three weeks old, and thus, developed shortly after vaccination. Tr. 24-25, 33-34, 60, 159-60. He suggested that Dr. Sriram's calculation using the size of the lesion as an indication of the length of time the lesion existed is incorrect; rather, the duration of enhancement correlates with size. Tr. 160-61. The fact that no black holes were noted on the MRI is further evidence that the lesions were not of long-standing duration. The actual enhancement pattern spoke to the relative newness of the lesions. Tr. 161-62.

Dr. Tornatore conceded petitioner could have had prior enhancing lesions in areas that did not cause perceivable symptoms until after the vaccination, and thus, the vaccine significantly aggravated her pre-existing brain lesions. Tr. 22-23, 33-36. Assuming the lesions existed before the vaccination, then "the tempo [of petitioner's symptoms] changed quite dramatically" and "symptomatically, we can see that." Tr. 33-36, 87. Regardless, he opined that the lesions could not all have been old because there was no long-standing inflammation seen in the CSF. Tr. 24-25.

Dr. Tornatore described radiologically isolated syndrome ("RIS"), which is where a patient has only non-enhancing lesions on an MRI, resulting from a prior inflammatory event that perhaps went unnoticed or unrecognized, and is asymptomatic. Tr. 58. In those patients, there is dissemination in space but not in time. Tr. 58. He distinguished those cases from petitioner's, stating that the CSF suggested something recent, and the ON emphasized that point. Tr. 59. "I'm

[42] Black holes are old lesions that are T1 positive and persist for six months or more. Tr. 100. Black holes are indicative of a loss of tissue due to inflammation. Tr. 101.

very, very convinced that there was an acute inflammatory event triggered by the vaccination and whether that may have been de novo or, otherwise, it was a very significant aggravation of a very low-grade inflammation that had been asymptomatic prior." Tr. 36, 59, 68, 87.

Dr. Tornatore then discussed petitioner's May 10, 2011 visit with Dr. Naalbandian. She had ON and was taking Copaxone for possible MS. Tr. 25-26; Pet. Ex. 2 at 242. The history on that date included onset two months prior with vision problems while driving, no viral illness or trauma to the head, no past neurologic events associated with MS, TM, cerebellar dysfunction or sensory motor abnormalities. Tr. 26-27; Pet. Ex. 2 at 242-43. Dr. Tornatore attributed little meaning to petitioner's report of minimal tingling in her feet while sitting, since it could be from sitting with legs crossed and because she was ambulatory. She did complain of more fatigue, though. He explained that over 50-60% of MS patients have fatigue thought to be due to immune activation and white blood cells producing cytokines and chemokines, "almost as if you have the flu." Tr. 27. She had only now developed fatigue, a fact that supported the relative newness of inflammatory activity. Tr. 27-28.

Dr. Tornatore next discussed the MRI on September 27, 2011. The disease was progressing with multiple new enhancing lesions, despite being treated with disease modifying therapy. At this point, she met the criteria for RRMS. Tr. 28-29; Pet. Ex. 2 at 5-6. Two months later, in November of 2011, she was clinically worse. She was ambulatory with occasional numbness in her left hand, and her motor function was normal. Tr. 30; Pet. Ex. 4 at 3.

Dr. Tornatore discussed petitioner's February 2012 visit with Dr. Minagar at LSU. She was still progressing clinically even though she was receiving Rebif injections three times a week. Tr. 31-32; Pet. Ex. 5 at 86-88. On examination, she had weakness in her legs and an unsteady, ataxic gait. Tr. 31-32; Pet. Ex. 5 at 87. Dr. Minagar admitted her for IV steroids. Tr. 31-32; Pet. Ex. 5 at 88. The diagnosis was RRMS. Tr. 32; Pet. Ex. 5 at 88.

Dr. Tornatore noted that on April 8, 2013—two years after her initial diagnosis of ON—her MRI was consistent with extensive MS with continuing development of new lesions some of which were still active. Tr. 33; Pet. Ex. 15 at 11-12. A December 18, 2019 MRI showed a "significant increase in the disease burden/number of demyelinating plaques since 2013. Multiple lesions show enhancement on the current exam, which is compatible with active demyelination." Tr. 34-35; Pet. Ex. 32 at 9-10. Six years later, petitioner continued to "accumulate new lesions, some are still active", thus demonstrating that her MS was not actively suppressed. Tr. 35. Her MRIs always showed active demyelination, even eight years since her illness started. Tr. 35.

He noted that the changes seen on her various MRIs speak to "a real significant change in the tempo of her symptoms starting in February of 2011", with no symptoms before that point. Tr. 33. Following her receipt of the subject vaccine, petitioner suffered episode after episode, was never asymptomatic at any time thereafter, and her MRIs progressively changed. Tr. 33-36, 87.

Because the lack of symptoms prior to the vaccine and her subsequent, progressively worsening condition immediately following the vaccine, the impact of the vaccine cannot be discounted. Tr. 88. He conceded that he has treated over 4,000 MS patients in over 30 years but never had one where a vaccine caused their MS. Tr. 56, 85. In fact, he agreed that there is no

known cause for MS. Tr. 55, 69-70. However, Dr. Tornatore maintained that in rare cases where there is an inflammatory event prior to the onset of MS symptoms, such as the vaccine here, one should not ignore it. Tr. 55, 69-70. "That's what's unique about this case, is that there really is a trigger that we can point to." Tr. 57.

3. Prong III

Dr. Tornatore stated that timing is "just really putting all the pieces together" as part of the larger clinical picture. Tr. 82-83. Dr. Tornatore agreed that *Cotton et al.* did not discuss ON, but focused instead on brain lesions; however, the study informed his opinion that petitioner's ON started within two weeks of the vaccination with enhancement of the optic nerve. Tr. 47, 82-83; Pet. Ex. 41.[43] The patients in *Cotton et al.* were given dye that leaked across the blood brain barrier and showed the lesions. The average duration of enhancement of new lesions was a median of two weeks and an average of three weeks. Tr. 47. Thus, "enhancement can come and go relatively quickly." Tr. 47. *Cotton et al.* also explained that smaller lesions enhance for a shorter amount of time. Tr. 72-73. According to Dr. Tornatore, an enhancing lesion is probably acute or about three weeks old, and a non-enhancing lesion could be less than three weeks old, but it is more difficult to determine its age. Tr. 48. Dr. Tornatore submitted that it is the duration of enhancement—not the intensity—that reveals how long the inflammation has been present. Tr. 70.

Dr. Tornatore maintained that it is unknown whether the non-enhancing lesions on petitioner's first MRI existed before the vaccine or developed after the vaccine but were not large enough to enhance. Tr. 72-73. However, he pointed to the fact that there was no inflammation in the CSF on March 28, 2011 and no prior symptoms as evidence that the onset of petitioner's MS occurred after the vaccine. Tr. 73-74. If there had been inflammatory markers in the CSF, she would have had ongoing symptoms for several months, which is expected in MS patients. Tr. 22, 48-49, 70. Though it is unclear how long it takes for oligoclonal bands to appear in the CSF, B cells must have time to cross the blood brain barrier, nest, and start producing oligoclonal bands, which is the hallmark of the chronicity in the brain. Tr. 74. Here, there were no bands and no white blood cells that go along with the IgG index, all indicating the acute nature of the onset. Tr. 74-75. All MS patients will develop increased white blood cells and oligoclonal bands in the CSF. The absence of oligoclonal bands in the CSF on March 28, 2011 is suggestive of the acute onset of petitioner's MS. Tr. 74-75. Here, "…I would argue, again, look at the totality of [petitioner's] clinical course and spinal fluid, which tells us that all this inflammation started just very, very, very close to when the vaccine was given." Tr. 61. "That's – what's so interesting about this case is that there is a defining event and that the spinal fluid really spoke to something that was new or nascent". Tr. 64. Further, Dr. Tornatore submitted that the tempo of her disease process, beginning shortly after vaccination and progressively worsening thereafter, cannot be ignored. Tr. 70-71, 73, 84-85.

Initially, Dr. Tornatore did not agree that there was evidence that petitioner had multiple brain lesions prior to the February 16, 2011 vaccination. Tr. 75. He then clarified that he was not

[43] Cotton et al., *supra* note 6.

opining on when the lesions presented on the brain because anything is possible; he stated that there are no absolutes in medicine. Tr. 75-76. Rather, based on the totality of petitioner's clinical presentation, symptoms, and MRI and CSF findings, his opinion was that the onset of petitioner's MS was acute following vaccination. Tr. 48-49, 76.

Dr. Tornatore concluded that petitioner's first hepatitis B vaccination primed the immune system, explaining the relatively fast 5-day manifestation of MS symptoms. When she received the second vaccine, she already had autoreactive T cells from the first that were boosted, causing a brisk immune response. Tr 45-46, 49. In support of his opinion on onset, he stated that the IOM recognized that a subsequent vaccination may lead to a more rapid immune response. Tr. 49. Based on scientific principles, sequence of cause and effect, and timing, it is his opinion that the hepatitis A/B vaccination caused or significantly aggravated petitioner's MS. Tr. 53.

b. Respondent's Expert, Dr. Subramaniam Sriram

i. Qualifications

Respondent's expert, Dr. Sriram, received his undergraduate degree at the University of Madras in Madras, India and his medical degree from Wayne State University in Detroit, Michigan. Resp. Ex. B at 1. He completed his residency in neurology and post-doctoral fellowship in neuroimmunology at Stanford University in Stanford, California. *Id.* He is a William Weaver Professor of Experimental Neurology and a Professor of Pathology, Microbiology, and Immunology at Vanderbilt University Medical Center ("VUMC") in Nashville, Tennessee. *Id.* at 2. Dr. Sriram is the head of the Multiple Sclerosis Clinic at VUMC and cares for "over 1000 adult and pediatric patients with MS." Resp. Ex. A.

ii. Expert Reports

As a preliminary matter, Dr. Sriram agreed that petitioner has RRMS. Resp. Ex. A at 2. He also agreed that MS is a clinical diagnosis based on evidence from clinical history, MRI findings, laboratory, and spinal fluid studies. He explained that "evidence for multiple events occurring at different times and at different sites of the central nervous system is a necessary pre-requisite for the diagnosis of MS." *Id.* According to Dr. Sriram, it's possible that there is damage to certain parts of the brain that does not produce neurological symptoms; in those scenarios, MS exists but can remain "clinically silent". *Id.*

Dr. Sriram described the abnormalities seen on MRI scans in MS patients. MRIs often show changes to the brain's white matter before clinical signs of MS present. Resp. Ex. A at 2-3. T2 lesions are white, hyperintense regions and T1 lesions are dark, hypointense regions. *Id.* at 2. When gadolinium is injected into the body, it seeps into the white matter of the brain. If lesions on the brain are active, they appear on an MRI as a bright signal. *Id.* All T2 lesions begin as T1 enhancing lesions, and enhancement generally lasts 1-10 weeks. *Id.* at 3. T2 lesions are typical for MS though nonspecific. *Id.* Dark, hypointense T1 lesions—or black holes—are seen as part of the active demyelinating process and in chronic inactive lesions which have undergone scarring. *Id.*

It is Dr. Sriram's opinion that, although petitioner first noted visual symptoms on or about February 21, 2011, the presence of T2 lesions on her first MRI suggested that these lesions preceded the receipt of the subject vaccination. Resp. Ex. A at 3. Thus, the vaccine did not cause petitioner's lesions to develop. Further, he submitted that there is no evidence that the hepatitis B vaccine can cause or significantly aggravate MS. Resp. Ex. Q at 3.

1. Prong I

According to Dr. Sriram, scientists have been studying a possible causal connection between the hepatitis B vaccine and MS for the past 25 years. Resp. Ex. A at 3. However, with all epidemiological evidence to date, there is no support for the notion that the hepatitis B vaccine can cause MS. *Id*.

Dr. Sriram described molecular mimicry as "immunological cross-reactivity in which patients develop an immune response to an environmental agent which cross reacts with a self-antigen resulting in autoimmune disease of the nervous system". Resp. Ex. A at 4. He submitted that the following criteria must be met to implicate molecular mimicry in the pathogenesis of disease: 1) the existence of a linear or conformational homology between a peptide of the environmental agent and a self-antigen 2) a cellular and/or antibody mediated immune response directed to the homologous peptide; 3) the presence of an immune response in patients with disease and the absence or reduced response in those without disease; 4) an immune response to the homologous peptide which results in organ specific damage; and 5) organ specific damage which results in disease. *Id*.

Dr. Sriram opined that there is no support that vaccines can induce autoreactivity that leads to the development of autoimmune diseases. Resp. Ex. A at 4; Resp. Ex. Q at 2. He agreed that MS is an inflammatory disorder of the CNS and that the prevailing opinion is that MS is mediated by an autoimmune process. However, he maintained that there is no evidence that autoreactivity to any of the myelin antigens of the CNS is present in MS. Resp. Ex. Q at 2. Multiple attempts to demonstrate specific autoreactivity to brain antigens to prove the autoimmune basis for MS have been unsuccessful, as researchers have not been able to find a biomarker or produce an immunological test for MS. *Id*. He noted that "the IOM could not find any evidence of cross reactivity between myelin proteins and hepatitis B antigen." *Id*. Further, there is no evidence that either the development of clinical worsening MS or an acute relapse of MS is causally connected to the receipt of vaccination; the causes of MS and its relapses are unknown. *Id*.

Dr. Sriram provided several reasons for why molecular mimicry between hepatitis B vaccine and MS is untenable. Resp. Ex A at 4. He submitted that there is no evidence that MS is caused by an immune response to myelin antigens and there is a lack of evidence that cross reactive peptides are responsible for the disease. *Id*. Additionally, he noted that if molecular mimicry existed between myelin antigens and hepatitis viral proteins, patients with chronic hepatitis infection would have continuous antigen stimulation of the immune system, placing them at high risk for MS. Yet, roughly one third of the world's population has been infected with hepatitis B

infection during their life and there is no evidence of an increased incidence of MS following infection. *Id*. at 4-5; Resp. Ex. Q at 3. Epidemiological studies have failed to show an association between hepatitis B and MS. Resp. Ex. A at 5; Resp. Ex. Q at 3. A recent Bavarian study showed no increased onset of MS between vaccinated and unvaccinated patients. Resp. Ex. V at 1; Resp. Ex. MM.[44] Other than the temporal relationship, there is no evidence that the hepatitis B vaccine can cause or exacerbate MS. Resp. Ex. Q at 3.

Dr. Sriram criticized Dr. Tornatore's reliance on *Gran et al*. *II*, stating that it was an abstract paper of a case study involving one patient who developed clinically definite MS after hepatitis B vaccination. Resp. Ex. Q at 2-3. The paper was not published in any peer reviewed journals, and there has not been any supportive evidence to demonstrate autoreactivity between the hepatitis B vaccine and myelin since then. *Id*.

Dr. Sriram concluded that "[t]he sum total of the analysis fails to support the notion of a causal connection between hepatitis B vaccine and the development of MS." Resp. Ex. A at 3.

2. Prong II

Dr. Sriram opined that petitioner's MS preceded her second hepatitis B vaccination, and the vaccination did not contribute to the development of or subsequent course of her MS. Resp. Ex. A at 5.

Dr. Sriram summarized petitioner's medical history, tests results, and MRI findings. He noted that the March 3, 2011 MRI showed "numerous abnormal T2 lesions with an appearance of distribution typical for demyelinating lesions associated with multiple sclerosis. A number of these lesions enhanced following injection of gadolinium." The MRI of the orbit showed "enlargement and enhancement of the optic nerve[s]" consistent with optic neuritis. Resp. Ex. A at 1; Resp. Ex. Q at 1; Pet. Ex. 2 at 1-3. Given the fact that T2 lesions are enhanced for approximately 1-10 weeks, Dr. Sriram submitted that it is likely that at least some of the T2 lesions seen on the first MRI existed prior to the subject vaccine. Resp. Ex. A at 3.

Even though petitioner appeared neurologically intact and asymptomatic prior to the hepatitis B vaccination, her brain was not normal. Resp. Ex. Q at 2. Dr. Sriram submitted that the lesions observed on the March 3, 2011 MRI predated the vaccine, and thus "she had radiological evidence of MS even prior to receipt of the vaccine." Resp. Ex. V at 1. Dr. Sriram concluded the hepatitis B vaccine petitioner received did not play a role in her development of MS. *Id*.

3. Prong III

Dr. Sriram did not dispute that petitioner's optic neuritis onset shortly after her receipt of the second hepatitis B vaccination. Resp. Ex. A at 3. Rather, he suggested that Dr. Tornatore relied on the temporal relationship between the vaccine and onset of petitioner's symptoms to provide his opinion. Dr. Sriram maintained there was no evidence the hepatitis B vaccine caused or exacerbated petitioner's MS. Resp. Ex. Q at 3.

[44] Subramaniam Sriram, MD & Israel Steiner, MD, *Experimental Allergic Encephalomyelitis: A Misleading Model of Multiple Sclerosis*, 58 ANN. NEUROLOGY 939 (2005), filed as "Resp. Ex. S" and "Resp. Ex. MM."

iii. Testimony

Dr. Sriram noted at hearing that he has published on MS but not on the relationship between MS and vaccines. Tr. 94. In his neurology practice, Dr. Sriram diagnoses and treats patients, and about 80% of his patients have MS. Tr. 95. He explained that a diagnosis of MS is based on the patient's history, neurological examination, and attendant laboratory and radiological data. Tr. 96, 109. Dr. Sriram agreed the criteria for diagnosing MS has evolved and is now less stringent. Tr. 96. Terms such as "probable" MS, "possible" MS, and "clinically isolated syndrome" are used less often at present. Tr. 96. The literature, including radiological literature, is important for treatment as well as diagnosis to help define abnormalities of the brain with certainty. Tr. 96-97. Epidemiology is not required to diagnose MS. Tr. 97.

Dr. Sriram described MS as a neurological disease of the central nervous system, characterized by destruction of myelin by the immune system. MS is restricted to the optic nerve, spinal cord, and brainstem.[45] Tr. 108, 129. MS has no known cause or antecedent events. Tr. 109. One school of thought as to the disease process of MS focuses on the pathology, which shows that the lymphocytes of the immune system target the central nervous system. The inflammatory effect attacks the myelin, leading to myelin destruction. Tr. 109-10. A brain biopsy will show that the blood brain barrier has been compromised with migration of lymphocytes and loss of myelin in large tracts. Tr. 110. The other school of thought maintains that the disease process is neurodegenerative with the inflammation reflective of the white cells and axons of the nervous system dying. Tr. 110. Therefore, most believe that there is either a neurodegenerative or a neuroinflammatory component, both, or that one evolves into the other. Tr. 110. However, the mechanism for what breaks down the blood brain barrier resulting in lesions is unknown. Tr. 111.

Dr. Sriram acknowledged that despite this controversy, only therapeutic medications that attack the inflammatory system, not the neurodegenerative system, exist. Tr. 110. Dr. Sriram added that statistically, there is a slight uptick in patients who have MS relapses from respiratory and urinary tract infections. These may be true relapses with enhancing lesions or pseudo relapses/recurrences of preexisting symptoms and signs. Tr. 105. MS patients who develop a secondary infection, such as a respiratory or bacterial urinary tract infection, are treated early because of the small percent who will relapse with an enhancing lesion. Tr. 105. Dr. Sriram testified that these are "the only infectious agent[s] that we know of that clearly [are] associated with a production of a relapse." Tr. 105.

Dr. Sriram described MS patients as having either relapsing remitting MS (70% of patients), primary progression MS, or radiologically isolated syndrome—a term rarely used any longer except in patients with optic neuritis where all other testing is normal. Tr. 98-99. Some patients with RIS develop RRMS, so their history must be analyzed retrospectively. For example, if a patient had ON in 2020 with a normal brain MRI but has lesions on the brain in 2030, then the ON is considered the first attack. Tr. 99-100.

[45] MS affecting the optic nerve causes vision issues, MS from the brainstem disrupts ocular motor function causing double vision, and MS from the spinal cord causes difficulty in ambulation and bladder and bowel function. Tr. 129. Ninety percent of lesions in MS are subclinical, and only 10% become eloquent. Tr. 129.

Dr. Sriram explained that CSF findings are positive in only 50-60% of patients in early MS, but they are positive in 95-97% in those with long term MS. However, CSF testing is not routinely done, and negative testing does not preclude a MS diagnosis. Tr. 102-03. Dr. Sriram explained that CSF testing has three components: white blood cells, oligoclonal bands, and spinal IgG index. The CSF is drawn from the spinal cord and is often negative unless there is inflammation of the cord. Tr. 103-04. Oligoclonal bands are not specific to MS, and oligoclonal bands and spinal IgG index can be elevated in other infectious diseases as well so neither is required for an MS diagnosis. Tr. 104.

1. Prong I

Dr. Sriram stated that there are no case studies, case reports, epidemiologic studies, or animal models with persuasive evidence that hepatitis B vaccine can cause MS. Thus, there is no evidence to support that the hepatitis B vaccine can cause or aggravate relapsing-remitting MS. Tr. 108, 111-15. Further, unlike other conditions that have defined antigens recognized in immunology as the cause of the condition,[46] there is no known cause for optic neuritis in MS.

Dr. Sriram described the various mechanisms resulting in autoimmunity. Molecular mimicry is an immune response to a host pathogen or self-antigen that leads to the inadvertent immune response against otherwise normal antigens. In the body's attempt to rid itself of the virus, antibodies to the self-protein are made, thus causing disease. Tr. 138-39. Bystander activation is when an immune response is amplified to a pathogen, a secondary amplification of other cells or bystander amplification can occur, resulting in autoimmunity. Tr. 139. Super antigens seen in bacterial infections amplify a whole clone of T cells and some inadvertently recognize human tissue, causing autoimmunity. Tr. 139.

Dr. Sriram submitted that animal models have not shown that hepatitis B virus can cause any disease that resembles MS. He noted that in the late 1980s, *Fujinami & Oldstone* studied rabbits injected with "hepatitis B polymerase" causing the rabbits to develop experimental allergic encephalitis. Tr. 140. The similarities between hepatitis B polymerase and myelin antigens resulted in what was "this novel idea of how molecular mimicry may happen." Tr. 140. However, Dr. Sriram noted that the study used polymerase which is antigenic,[47] while the hepatitis B vaccine antigen is not antigenic. Tr. 115.

Gran et al. I, which was published after the *Fujinami & Oldstone* study, showed cross-reactivity between an antigen of hepatitis B polymerase and certain myelin antigens. However, Dr. Sriram again pointed out that petitioner received the hepatitis B antigen—not the hepatitis B polymerase used in the study. Tr. 140-41; Pet. Ex. 44.[48] Thus, it was his opinion that the results of the *Gran et al. I* study cannot be extrapolated to the facts here. Tr. 141. However, he acknowledged that he has not looked at the entire sequence to see if there is homology between the antigen and the polymerase. Tr. 141. To his knowledge, no further studies have since been published corroborating the findings in *Gran et al. I*. Tr. 142.

[46] For example, neuromyelitis optica is caused by antibodies to Aquaporin-4 antigen or anti-MOG antibodies. Tr. 125-26.
[47] Antigenic refers to something that has the properties of an antigen. *Dorland's* 105.
[48] Gran, MD, et al., *supra* note 20.

Over 30 years have passed since *Fujinami & Oldstone*, and there remains little evidence that molecular mimicry plays a role in human autoimmunity. Tr. 140. The evidence is insufficient to show that a viral protein can cross react with a myelin antigen. In MS, it is even harder to demonstrate molecular mimicry because the myelin antigen involved in MS is unknown. Tr. 140. Dr. Sriram argued that all attempts to show cross reactivity have been flawed because they assume that the CNS proteins—MBP, PLP, and MOG—are pathogenic in MS, but that remains unknown. Tr. 140.

Dr. Sriram disagreed with Dr. Tornatore's position that the IOM found that there is a biological basis that hepatitis B vaccine could lead to demyelination. Tr. 142-43; Pet. Ex. 22 at 3; Pet. Ex. 42.[49] Dr. Sriram quoted the IOM report stating: "Amino acid homology between myelin basic protein and the hepatitis B virus polymerase has been reported. In addition, an injection of the HBV polymerase epitope shared with MBP into rabbits resulted in EAE-like disease. However, infection of hepatitis B is not associated with the development of demyelinating disease. Furthermore, the recombinant vaccine contains hepatitis B surface antigen and not hepatitis B virus polymerase."[50] Tr. 143.

Dr. Sriram added that there is inconclusive evidence that molecular mimicry between hepatitis B vaccine proteins and CNS antigens play a role in MS. He submitted that there is no significant homology between the amino acid sequences of the hepatitis B surface antigen—the main component of the hepatitis B vaccine—and the myelin proteins MOG, MOG, MBP and PLP. Dr. Sriram stated "this makes it unlikely that a T-cell mediated immune response against these CNS autoantigens would be triggered by the hepatitis B vaccine on the basis of molecular mimicry." Tr. 144; Pet. Ex. 42.[51] Dr. Sriram further stated that the presence of autoreactivity to MOG or PLP is insufficient until there is some evidence that these peptides are causing some aspect of MS. Tr. 144.

Dr. Sriram referenced the *Schirmer et al.* paper, in which the authors did not find any autoantigens in MS. Tr. 145; Resp. Ex. NN.[52] In 2014, the authors concluded that despite continuous improvement in screening and validation, no MS specific autoantibody has been established and broadly validated "until today." Tr. 145. For Dr. Sriram, it is difficult to sustain an argument of molecular mimicry without defined autoantigens. Tr. 145.

In contrast, Dr. Sriram offered that rabies and smallpox vaccines can cause demyelinating disease. Tr. 147. There is also sufficient evidence in animal studies showing that cross reactivity

[49] Institute of Medicine 2002, *supra* note 17.
[50] Dr. Sriram read this passage from the IOM report into the record at hearing. However, upon review of the literature filed, this passage cannot be located in either IOM report that was filed in this matter. *See* Resp. Ex. U; Resp. Ex. OO. Petitioner filed a separate IOM report, which discussed evidence from animal models on the role of hepatitis B vaccine in demyelination. In that report, the IOM concluded that there is no evidence that exposure to the hepatitis B vaccine leads to EAE based on evidence from a 1985 study where rabbits were immunized with the HBV polymerase and did not develop EAE. *See* Pet. Ex. 42 at 7-8. However, it remains unclear whether this is the article Dr. Sriram was referring to in his testimony because the passage he quoted cannot be found in it either.
[51] Institute of Medicine 2002, *supra* note 17.
[52] Lucas Schirmer et al., *To Look for a Needle in a Haystack: The Search for Autoantibodies in Multiple Sclerosis*, 20(3) MULTIPLE SCLEROSIS J. 271 (2014), filed as "Resp. Ex. T" and "Resp. Ex. NN."

can cause GBS with molecular mimicry between lipid oligosaccharide present on the myelin membrane. However, Dr. Sriram posited that "there is no cross-reactivity to protein epitopes causing autoimmunity in man. There are in animals, yes, not in man." Tr. 147-48. Further, transverse myelitis is a heterogeneous disease that could have an infectious, traumatic, or autoimmune cause or can be part of the "MS picture", and it is characterized by inflammation of the spinal cord. Tr. 148. Dr. Sriram has not researched it himself, but he believed the evidence to be insufficient to support any vaccine causing TM, as there are no clinical reports, clinical case studies, epidemiology, or animal models to show an association. Tr. 148-49.

Dr. Sriram relied on *Brex et al.* to support his position that lesions can exist without symptoms. Of the patients studied in *Brex et al.*, 50-70% had evidence of brain lesions but were asymptomatic. Tr. 136-37; Resp. Ex. LL.[53] In people with ON or RIS who presented years later with another attack, it was the same disease but was now disseminated in space and time. Tr. 137. Of the patients with normal MRIs for 14 years, many had abnormal MRIs by the end of the study. Tr. 137-38.

Dr. Sriram referenced three studies—*Hapfelmeier et al.*, *Asherio et al.*, and *Confavreux et al.*—to support his opinion that vaccines are protective for MS patients. Tr. 113-14, 152-53; Resp. Ex. PP;[54] Resp. Ex. BB;[55] Resp. Ex. HH.[56] *Hapfelmeier et al.* included a large sample of 10,000-12,000 people with confirmed MS whose vaccination records were reviewed. Contrary to expectation, those who received the hepatitis vaccine were less likely to develop MS, thus suggesting the vaccine's protective effect. Tr. 113-14; Resp. Ex. PP.[57] *Ascherio et al.* looked at records from the Kaiser health system and found no increase in MS following hepatitis B vaccination. Tr. 135-36; Resp. Ex. BB.[58] Finally, *Confavreux et al.* studied 38 patients for MS relapses after receiving the hepatitis B vaccine and the authors, like *Hapfelmeier et al.*, found relapse was less likely with vaccination. Tr. 134; Resp. Ex. HH.[59] Dr. Sriram also offered the *Zipp et al.* article, in which 27,000 vaccinated patients were compared to 107,000 nonvaccinated patients and the authors found no evidence that the hepatitis B vaccine increased the likelihood of development or relapse of MS. Tr. 135; Resp. Ex. AA.[60]

Dr. Sriram disagreed that the hepatitis B vaccine can trigger inflammation of the optic nerve or cause or aggravate MS. Tr. 146. He agreed that a correlation between hepatitis B vaccine and MS has been studied for the past 30 years—and continues to be studied today—but stated that an association has not been proven or disproven because it is so rare. Tr. 151, 154. However, he disagreed that there is concern over the potential correlation between the two. Tr. 154. Dr. Sriram

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[53] Peter A. Brex, M.D., et al., A Longitudinal Study of Abnormalities on MRI and Disability from Multiple Sclerosis, 346 NEW ENG. J. MED. 158 (2002), filed as "Resp. Ex. R" and "Resp. Ex. LL."

[54] Alexander Hapfelmeier, PhD, et al., *A Large Case-Control Study on Vaccination as Risk Factor for Multiple Sclerosis*, 93 NEUROLOGY 908 (2019), filed as "Resp. Ex. W" and "Resp. Ex. PP."

[55] Alberto Ascherio, M.D., Dr.P.H., et al., *Hepatitis B Vaccination and the Risk of Multiple Sclerosis*, 344 NEW ENG. J. MED. 327 (2001), filed as "Resp. Ex. G" and "Resp. Ex. BB."

[56] Christian Confavreux, M.D., et al., *Vaccinations and the Risk of Relapse in Multiple Sclerosis*, 344 NEW ENG. J. MED. 319 (2001), filed as "Resp. Ex. M" and "Resp. Ex. HH."

[57] Hapfelmeier, PhD, et al., *supra* note 54.

[58] Ascherio, M.D., Dr.P.H., et al., *supra* note 55.

[59] Confavreux, M.D., et al., *supra* note 56.

[60] Frauke Zipp, et al., *No Increase in Demyelinating Diseases After Hepatitis B Vaccination*, 5 NATURE MED. 964 (1999), filed as "Resp. Ex. F" and "Resp. Ex. AA."

agreed that epidemiology cannot prove a negative, particularly when the association is rare. Tr. 155-56. However, he clarified that "we do not know what the baseline rare association—is it—how much is it, 1 in 1,000, 1 in 10,000 for us to make some kind of epidemiological study." Tr. 156. He agreed that there are people who can live their entire lives without symptoms of MS but have lesions consistent with MS on autopsy. Tr. 156. Dr. Sriram stated that based on case reports, epidemiology, and animal models, there is no evidence that would lead him to conclude that the hepatitis B vaccine caused the onset of optic neuritis or brain lesions that manifested as MS in petitioner. Tr. 154.

According to Dr. Sriram, he treats MS patients with fulminant optic neuritis all the time in his practice and is consistently unable to tell them what triggered or caused the event. However, he will not attribute it to an event such as a vaccine just because that is the only antecedent event. Tr. 150-51. "It doesn't mean that [a vaccine] couldn't have, it's just that you don't know." Tr. 151.

2. Prong II

In Dr. Sriram's opinion, petitioner's brain lesions were present prior to the February 16, 2011 hepatitis A/B vaccination, so the vaccine did not cause or aggravate her MS. Tr. 108, 111, 131-32. Further, there is no evidence that hepatitis B vaccine is associated with the development or aggravation of MS; thus, petitioner's hepatitis B vaccine should not be implicated in her disease process. Tr. 108, 111-15; Resp. Ex. Q at 3.

Dr. Sriram stated that he has attended courses, seminars, and educated himself on reading MRIs, and he reads the MRIs of his MS patients 3-4 times daily in his practice. Tr. 97-98. He described the main signals seen on MRIs of MS patients. A T2 flare shows the area of whiteness in the white matter. A T1 flare is enhanced or active when gadolinium is injected. A T1 flare that is not enhanced with gadolinium is typically an old lesion; if they persist for six months, these are called black holes. Tr. 100. A T1 black hole shows a loss of tissue resulting from inflammation. Tr. 100-01. T1 black holes are lesions that were enhanced at some point in time for at least 8 to 12 weeks showing long standing inflammation. When black holes are seen, there is concern for a more destructive process and the need for aggressive therapy. T1 black holes are used to ascertain the intensity and severity of the disease. Tr. 100-01.

Dr. Sriram referenced C*otton et al.* in support of his opinion on the duration of brain lesions. He explained that lesions are measured by voxels, which are small pixels on an MRI. A voxel greater than 100 indicates that a lesion has existed for 12 weeks or more. Tr. 102, 120-21; Resp. Ex. X.[61] He pointed to Figure 2 in *Cotton et al.* explaining that there is a linear line; the X axis is the duration of enhancement, and the Y axis is the volume of the lesion, which is calculated as voxels. Tr. 121; Pet. Ex. X at 4, Figure 2. The larger the lesion, the longer the duration. Larger lesions last up to 14 weeks. Tr. 122.

Petitioner's March 3, 2011 MRI report documented "numerous" areas of T2 prolongation in the intermediate periventricular white matter. Dr. Sriram interpreted the term "numerous" as more than five. Tr. 117; Pet. Ex. 2 at 1-2.

[61] Cotton et al., *supra* note 6.

He opined that the non-enhancing lesions on petitioner's first MRI were 6-12 weeks old. Tr. 119. Therefore, at least some of the lesions were present before the February 16, 2011 vaccination. Tr. 123-24. The non-enhancing T2 lesions were "by no means small" and had an enhancement period that exceeded two weeks. Tr. 124. The enhancement/non-enhancement and size of the lesions were consistent with MS that predated the vaccine. Tr. 123-24. Further, there were no black holes. Tr. 119-20.

According to Dr. Sriram, petitioner exhibited the classic features of RRMS. The March 3, 2011 MRI of the right orbit showed diffuse enhancement of the optic nerve, confirming the clinical impression of optic neuritis typical in MS patients. Tr. 125; Pet. Ex. 2 at 3. It is highly unlikely that a lesion is present on the optic nerve without symptoms. Tr. 126-27. When ON is a result of MS, it involves the central part of the visual nerve affecting vision—specifically, the macular fibers that control acuity and color, the most sensitive being red. Tr. 127. Dr. Sriram agreed that optic neuritis was the defining event for petitioner's MS, with onset 5 days after her vaccination. Tr. 128-30. The visual problems and enhancing lesions seen on the March 3, 2011 MRI were "one common pathological process." Although it was unknown whether there was any swelling of the optic nerve on February 21, 2011, Dr. Sriram could say with a fair degree of confidence that petitioner's MS began with the seminal event of inflammatory changes in the optic nerve five days after she received the subject vaccine. Tr. 130-32.

Dr. Sriram stated that petitioner's March 3, 2011 MRI "cemented the diagnosis" of MS with dissemination in space and time showing enhancing lesions on the optic nerve and on the brain, as well as non-enhancing lesions. Thus, petitioner satisfied the criteria for clinical MS. Tr. 132.

Dr. Sriram did not find it significant that petitioner had normal CSF results on March 28, 2011. Tr. 132-33; Pet. Ex. 2 at 12. He testified that only 50-60% of MS patients have oligoclonal bands in early MS. Tr. 133. The lack of oligoclonal bands does not preclude an MS diagnosis. Tr. 133. All that is required to diagnose RRMS is dissemination in space and time, which petitioner had. Tr. 133.

Succinctly, Dr. Sriram agreed with petitioner's diagnosis of RRMS. Tr. 133. He also agreed that the first manifestation of her MS occurred five days after she received the vaccine. Tr. 128-30. However, he maintained that the lesions on her brain were present prior to the vaccine and the vaccine did not play a role in causing or significantly aggravating her MS. Tr. 108, 111, 123-24, 131-32.

3. Prong III

Dr. Sriram agreed that the onset of an inflammatory process started five days after vaccination and that the March 3, 2011 MRI contained enhancing lesions. Tr. 149-50. However, he suspected that if an MRI had been done prior to vaccination, lesions on petitioner's brain would have been observed. Tr. 149-50. Although Dr. Sriram agreed that petitioner was asymptomatic until five days after receipt of the hepatitis B vaccine, he finds it "highly unlikely" the vaccine caused an inflammatory process that caused or significantly aggravated those lesions. Tr. 150.

VI. Applicable Law

a. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *See Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[62]

To prove causation for an "off-Table" injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id*. at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioner to provide a "reputable medical theory" demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable,

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

not medically or scientifically certain." *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548); *see also Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

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

To satisfy the third *Althen* prong, petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

A petitioner may also be eligible for compensation if the vaccinee had a preexisting condition which was significantly aggravated by a vaccine. *See* § 11(c)(1)(C). In considering a significant aggravation claim for an on-Table injury, the Federal Circuit placed the most significance on whether petitioner's symptoms began within the time period proscribed. *Whitecotton v. Sec'y of Health & Human Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996) ("Instead of asking whether the person's symptoms would have occurred absent the vaccine, our test hoves (sic) close to the statutory mandate, and relieves a petitioner of the burden of proving causation if she can show that the first symptom or manifestation of the significant aggravation of her condition occurred within the table time period provided in the statute.").

For a significant aggravation claim for an off-Table injury, the petitioner's burden is expanded to six elements, requiring petitioner to show, by preponderant evidence, proof of

> (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 ex rel. Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). The fourth, fifth, and sixth factors are derived from *Althen* prongs one, two, and three, respectively. *Id*. The Federal Circuit has agreed with this approach. *See W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) ("We hold that the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims.")

However, the third *Loving* factor, determining whether the person suffered a "significant aggravation" of his or her condition, leads to the question of what constitutes a significant aggravation. Based on the legislative history and the language of the statute, it appears that Congress intended for a "significant aggravation" of a condition to present rather dramatically. *See* H.R. Rep. 908, 99th Cong.2d Sess. 1, reprinted in 1986 USCCAN 6287, 6356 ("This [significant aggravation] provision does not include compensation for conditions which might legitimately be described as preexisting (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)); *see also* 42 U.S.C. § 300aa-33(4) ("The term "significant aggravation" means any change for the worse in a preexisting condition which results in *markedly greater* disability, pain, or illness accompanied by *substantial deterioration* of health" (emphases added)).

Once a petitioner has established that his or her condition worsened post-vaccination, the special master must determine "whether the change for the worse in [petitioner's] clinical presentation was aggravation or a natural progression" of the preexisting condition. *Hennessey*, 2009 WL 1709053 at *42. In doing so, special masters have relied on evidence supporting the "typical" clinical course of the petitioner's condition. *See, e.g.*, *Sharpe v. Sec'y of Health & Human Servs.*, 964 F.3d 1072, 1086 (Fed. Cir. 2020) (Special master's determination that petitioner failed to meet *Loving* prong 5 because her seizures began prior to vaccination was set aside); *Faoro v. Sec'y of Health & Human Servs*., No. 10-704V, 2016 WL 675491, at *27 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. for review denied*, 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").

b. Legal Standard Regarding Fact Finding

The process for making determinations in Vaccine Program cases regarding factual issues begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are generally considered to be more trustworthy. *Cucuras v. Sec'y of Health & Human Servs*., 993 F.2d 1525,

1528 (Fed. Cir. 1993); *but see Kirby v. Sec'y of Health & Human Servs*., 993 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying that *Cucuras* does not stand for proposition that medical records are presumptively accurate and complete). While not presumed to be complete and accurate, medical records made while seeking treatment are generally afforded more weight than statements made by petitioner after-the-fact. *See Gerami v. Sec'y of Health & Human Servs*., No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013) (finding that contemporaneously documented medical evidence was more persuasive than the letter prepared for litigation purposes), *mot. for rev. denied*, 127 Fed. Cl. 299 (2014). Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co*., 333 U.S. 364, 396 (1948).

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining facts such as the onset of a petitioner's symptoms. *Vallenzuela v. Sec'y of Health & Human Servs*., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); *see also Eng v. Sec'y of Health & Human Servs*., No. 90-175V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb 18, 1994) (explaining that § 13(b)(2) "must be construed so as to give effect to § 13(b)(1) which directs the special master or court to consider the medical record...but does not require the special master or court to be bound by them"); *see also Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (holding that it is within the special master's discretion to determine whether to afford greater weight to medical records or to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is rational).

There are situations in which compelling oral testimony may be more persuasive than written records. *See Campbell*, 69 Fed. Cl. at 779. When witness testimony contradicts medical records, such testimony must be consistent, clear, cogent, and compelling to be persuasive. *See Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (vacated on other grounds, *Sanchez by & through Sanchez v. Sec'y of Health & Human Servs*., No. 2019-1753, 2020 WL 1685554 (Fed. Cir. Apr. 7, 2020), *review denied, Sanchez by & through Sanchez v. Sec'y of Health & Hum. Servs*., 152 Fed. Cl. 782 (2021)) (quoting *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *85 (Fed. Cl. Spec. Mstr. June 30, 1998)); *see, e.g., Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs*., No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). Special masters may also consider other types of evidence, such as unsworn statements, on the grounds that the Vaccine Program was designed to have "flexible and informal standards of admissibility of evidence." 42 U.S.C. § 300aa-12(d)(2)(B); *see also Munn v. Sec'y of Health & Human Servs*., 970 F.2d 863, 873 (Fed. Cir. 1992).

In short, "the record as a whole" must be considered. § 13(a).

c. Evaluating Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of*

Health & Human Servs., 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

d. Consideration of Medical Literature

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

VII. Discussion

Petitioner does not allege an injury listed on the Vaccine Injury Table, therefore her claim is classified as "off-Table." As noted above, for petitioner to prevail on an "off-Table" claim, she must show by preponderant evidence that her injury resulted from the vaccination at issue. *Capizzano*, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that the injury was caused by factors unrelated to the vaccination(s). *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013). To meet his burden, respondent must show by preponderant evidence that the injury alleged is "due to factors unrelated" to the vaccine. § 13(a)(1)(B). The Vaccine Act states that the term "factors unrelated" does not include "any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition." § 13(a)(2)(A).

Because an issue exists as to whether petitioner's MS was caused or significantly aggravated by the hepatitis A/B vaccination, she must carry her burden not only on the three *Althen* prongs, but also on the three additional prongs of *Loving*. In sum, petitioner must show 1) a medical

theory causally connecting the hepatitis A/B vaccine with her MS, 2) a logical sequence of cause and effect between the hepatitis A/B vaccine and MS, and 3) an appropriate temporal relationship between the hepatitis A/B vaccine and the onset of her symptoms. Then she must demonstrate that 4) she had pre-existing asymptomatic MS 5) that evolved into symptomatic MS 6) which is clearly a significant aggravation of her pre-existing condition under the *Loving* criteria.

a. *Althen* Prong 1/*Loving* Prong 4: Petitioner Has Provided a Reputable Medical Theory for How a Hepatitis A/B Vaccine Can Significantly Aggravate Asymptomatic Multiple Sclerosis.

Dr. Tornatore opined that the hepatitis A/B vaccine can either cause MS or significantly aggravate pre-existing, asymptomatic MS through molecular mimicry. Tr. 36, 59, 68, 87. In contrast, Dr. Sriram argued that there is insufficient evidence that the hepatitis B vaccine can cause or aggravate MS. Tr. 108, 111-12.

Both experts relied in part on IOM reports to support their opinions on whether the subject vaccine can cause or significantly aggravate MS. Tr. 37-38, 142-43; Pet. Ex. 22 at 3; Resp. Ex. Q at 2. The 2002 IOM report noted that there was considerable evidence that demyelination in the CNS with diseases like MS was the result of inflammatory, immune mediated processes. *See generally* Pet. Ex. 42.[63] The initial event in the formation of MS lesions appeared to be activation of autoreactive T cells. *Id*. at 4. The IOM pointed out that there are several autoantigens within the brain, including MOG and PLP, that could trigger the activation of T cells. *Id*. The report then discussed the mechanisms that could account for the activation of self-reactive T and B cells and the induction of autoimmunity: molecular mimicry, bystander activation, and non-specific or polyclonal activation of self-reactive T or B cells. *Id*. The IOM concluded that "[i]t is conceivable that antigenic stimulation from vaccines could trigger any of these potentially damaging mechanisms. There is no reason in theory why *hepatitis B surface antigen* in the vaccine could not function in this way. Thus, there is a theoretical basis for a hepatitis B vaccine-induced immune response that could possibly lead to demyelination." *Id*. at 7 (emphasis added). However, the IOM cautioned that the evidence is scant and indirect. *Id*.

The 2002 IOM report also discussed animal studies of EAE in mice and rats compared to human demyelinating diseases like MS as providing a strong indication that immunization with certain antigens can trigger autoimmune processes resulting in demyelinating injuries. Pet. Ex. 42 at 7-8.[64] However, there is no evidence that exposure to the hepatitis B vaccine containing only one protein, HBsAg, leads to EAE. *Id*. at 7. Specifically, the IOM referenced the *Fujinami & Oldstone* study on rabbits using HBV polymerase, which shares six consecutive amino acids with myelin basic protein. *Id*. at 7-8. The IOM stated that the findings have largely been interpreted as evidence that the hepatitis B vaccine could cause demyelination, thus proposing molecular mimicry as a viable causation theory. *Id*. at 8; Tr. 115, 140. Dr. Sriram pointed out that the IOM stated that hepatitis B polymerase is not similar to the hepatitis B surface antigen used in the current

[63] Institute of Medicine 2002, *supra* note 17.
[64] *Id*.

vaccine. Pet. Ex. 42 at 8; Tr. 115, 140. Dr. Sriram clarified that polymerase is antigenic, while hepatitis B vaccine is not antigenic. Tr. 115.

Dr. Sriram highlighted the IOM committee's conclusion that "there is no significant homology between the amino acid sequences of HBsAg, the main component of hepatitis B vaccine, and the myelin proteins MOG, MBP, and PLP." Pet. Ex. 42 at 8;[65] Tr. 144. Therefore, the IOM determined it is unlikely that a "T cell-mediated immune response against these CNS autoantigens would be triggered by the hepatitis B vaccine on the basis of molecular mimicry." Pet. Ex. 42 at 8. The IOM added that while humoral autoimmune response is still conceivable, no antibody against HB virus, specifically against HBsAg, has been identified in MS. *Id*. at 9. It recognized that some evidence exists that the hepatitis B vaccine is associated with an autoimmune-mediated form of alopecia, but the pathophysiological similarities between alopecia and demyelinating conditions is not strong enough to establish a causal relationship. *Id*. Thus, there is only "weak evidence of biological mechanisms relevant to the immune-mediated neurological outcomes". *Id*. Based on these findings, Dr. Sriram submitted that there is insufficient evidence to support a link between the hepatitis B vaccine and MS. Tr. 111, 140, 144, 149. He maintained that the cause of MS remains unknown, although he conceded that MS is believed to be autoimmune. Tr. 111; Resp. Ex. Q at 2. Dr. Sriram opined that because the cause of MS is unknown, its association with hepatitis B virus or vaccine is unsupported by scientific evidence. Tr. 145.

Nevertheless, the IOM explained that when an infectious agent has been associated with a particular adverse health outcome, the possibility exists that the vaccine against that agent can have a similar effect. Pet. Ex. 42 at 9.[66] Anecdotal reports document an association between acute infection and MS. *Id*. The IOM noted that several viruses like Epstein Barr are risk factors for both MS and relapses, but the hepatitis B virus is "not prominent in the discussions of viral triggers." *Id*. Similarly, Dr. Sriram submitted that the only thing known about MS, which is more "statistical," is that there is a "slight up-tick" in MS relapses following respiratory infection and bacterial urinary tract infection. Tr. 105.

Dr. Tornatore relied on the IOM findings to support his opinion that "there is a theoretical basis for hepatitis B vaccine induced immune response that could possibly lead to demyelination", though he acknowledged that the IOM stated the evidence is "scant and indirect." Tr. 37-38; Pet. Ex. 42 at 7.[67]

Dr. Tornatore also discussed two papers by *Gran et al*. The authors in *Gran et al. I* found that sequence homology between self and foreign antigens may not need to be identical for cross recognition to occur. Tr. 41-43; Pet. Ex. 44.[68] Dr. Sriram conceded that *Gran et al. I* showed that an antigen of hepatitis B polymerase cross reacted with certain myelin antigens, while noting that petitioner received the hepatitis B antigen—not the hepatitis B polymerase. Tr. 140-41; Pet. Ex. 44.[69] However, Dr. Sriram acknowledged that he has not looked at the entire sequence to see if there is homology between the antigen and the polymerase. Tr. 141.

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[65] *Id*.
[66] *Id*.
[67] *Id*.
[68] Gran, MD, et al., *supra* note 20.
[69] *Id*.

The second paper, *Gran et al. II*, was a case study of a patient who developed MS three months following hepatitis B vaccination. The authors found cells that responded to both the hepatitis B surface antigen and myelin basic protein in both the blood and CSF of the patient. Based on the findings, the authors concluded that molecular mimicry after hepatitis B vaccination warrants further investigation as a possible trigger of autoimmune demyelination. Tr. 39-41; Pet. Ex. 43.[70] In discussing *Gran et al. II*, the IOM explained that it described onset of clinically definite MS after hepatitis B vaccination. Pet. Ex. 42 at 8.[71] Dr. Tornatore cited to both papers by *Gran et al*. as evidence that the hepatitis B vaccine can trigger MS through molecular mimicry, even in the absence of exact sequence homology. Pet. Ex. 18 at 16; Pet. Ex. 22 at 5; *see also* Pet. Ex. 43;[72] Pet. Ex. 44.[73]

Further, the *Bogdanos et al.* article, which used the hepatitis B surface antigen, demonstrated cross-reactivity between at least one surface antigen and myelin protein. Tr. 44, 157-59; Pet. Ex. 45 at 1.[74] Like *Gran et al. II*, *Bogdanos et al.* concluded that the "vaccine's possible role as an immunomodulator of viral/self cross-reactivity must be further investigated." Tr. 45; Pet. Ex. 45 at 1.[75] Based on the aforementioned literature, Dr. Tornatore submitted that "it is not only plausible, but it's scientifically demonstrated" that the hepatitis B vaccine is linked to MS. Tr. 37-38, 80.

Dr. Sriram submitted that case studies show there is no support for an association. *Hapfelmeier et al.* studied 10,000-12,000 patients with MS who received a hepatitis B vaccination and unexpectedly found the vaccine to have a protective effect. Tr. 113-14; Resp. Ex. PP.[76] *Ascherio et al.* and *Confavreux et al.* studied relapses after hepatitis B vaccination, and like *Hapfelmeier et al.*, found there was a lesser chance of developing MS with receipt of the hepatitis vaccine. Tr. 113-14, 134-36; Resp. Ex. BB;[77] Resp. Ex. HH.[78] Similarly, *Zipp et al.* compared 27,000 vaccinated patients with 107,000 unvaccinated patients and found no evidence of hepatitis B vaccine increasing the development of MS or MS relapses. Tr. 135; Resp. Ex. AA.[79] Dr. Sriram also pointed to *Schirmer et al.*, which concluded that no MS-specific autoantibody has been established and broadly validated "until today." Tr. 145; Resp. Ex. NN at 7.[80] It is unclear what "until today" refers to. Based on this finding, Dr. Sriram stated it is difficult to sustain an argument of molecular mimicry. Tr. 145.

In summary, Dr. Sriram stated that "[t]here is inconclusive evidence that molecular mimicry between hepatitis B vaccine proteins and CNS antigens plays a role, or even exists, in the

[70] Gran et al., *supra* note 25.
[71] Institute of Medicine 2002, *supra* note 17.
[72] Gran et al., *supra* note 25.
[73] Gran, MD, et al., *supra* note 20.
[74] *Id.*
[75] *Id.*
[76] Hapfelmeier, PhD, et al., *supra* note 54.
[77] Ascherio, M.D., Dr.P.H., et al., *supra* note 55.
[78] Confavreux, M.D., et al., *supra* note 56.
[79] Zipp, et al., *supra* note 60.
[80] Schirmer et al., *supra* note 52.

pathogenesis of MS." Tr. 144; Pet. Ex. 42 at 8.[81] Further, "there is no significant homology" between the hepatitis B surface antigen and myelin proteins, thus making molecular mimicry between the two unlikely. Tr. 144; Pet. Ex. 42 at 8. His opinion is based on the fact that there are no clinical reports, case studies, animal models, or epidemiology to support an association between the hepatitis B vaccine and MS. Tr. 149.

Petitioner's burden in establishing whether the hepatitis A/B vaccine can cause or aggravate MS requires that petitioner provide a reputable medical theory linking the vaccine to the injury alleged. *See Pafford*, 451 F.3d at 1355-56 (citation omitted). I find that preponderant evidence supports the theory that the hepatitis B vaccine can significantly aggravate pre-existing MS.

Demyelinating diseases, whether genetically or environmentally caused, result from the body attacking itself and stripping away the myelin sheath that protects the nerves. Tr. 108, 129. Dr. Sriram agreed that MS is considered a demyelinating disease, and that vaccines can cause some demyelinating diseases on the basis of cross-reactivity. Tr. 147-49. The experts also agreed that research into a link between the hepatitis B vaccine and MS has been ongoing for over 30 years and continues today. Tr. 77-81, 151.

While Dr. Sriram is correct that the IOM rejected an explicit causal relationship between the hepatitis B vaccine and MS and MS relapses based on the lack of epidemiological studies, he seemed to discount the IOM's conclusion in 2002 that there is a theoretical basis explaining how the hepatitis B vaccine could induce an immune response that leads to demyelination. Pet. Ex. 42 at 7.[82] Although the IOM issued another report a decade later, there was no indication in the 2012 IOM report that the conclusions in 2002 were invalidated or no longer supported. *See* Resp. Ex. U.[83]

The 2002 IOM committee also noted that infection is a risk factor for MS and MS relapses. Pet. Ex. 42 at 9.[84] Dr. Sriram acknowledged a statistical increase in MS relapses following infection. Tr. 105. Further, the IOM concluded that a vaccine can act like an infection. Pet. Ex. 42 at 9. Thus, it follows that a vaccine could evoke a similar response to an infection and incite an MS event. *Id*. Even with clinically silent MS, "an inflammatory event" is needed to trigger MS symptoms in a patient who has MS but is asymptomatic. Tr. 64.

Dr. Sriram cited to *Schirmer et al.* to support his contention that molecular mimicry is not a reliable theory for the cause or aggravation of MS because no MS specific autoantibody has been established. Tr. 145. However, the authors in *Schirmer et al.* concluded that "no MS-specific autoantibody has been established and broadly validated *until today*." Resp. Ex. NN at 7 (emphasis added). [85] They explained the difficulty in identifying the autoantibodies in prior studies, but then stated that "recent studies propose interesting targets that are currently undergoing the evaluation

[81] Institute of Medicine 2002, *supra* note 17.
[82] *Id.*
[83] Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality*, Nat'l Academic Press (2012) [hereinafter "Institute of Medicine 2012"], filed as "Resp. Ex. U" and "Resp. Ex. OO."
[84] Institute of Medicine 2002, *supra* note 17.
[85] Schirmer et al., *supra* note 52.

and validation process." *Id*. Thus, Dr. Sriram is correct that an MS-specific autobody has not yet been conclusively established; however, the authors in *Schirmer et al.* suggest that the targets have been identified and are currently under review.

Further, as demonstrated by *Gran et al. I*, exact homology between a foreign antigen and myelin protein is unnecessary for molecular mimicry to occur. Tr. 41-43; Pet. Ex. 44.[86] Dr. Sriram did not find *Gran et al. I* to be persuasive, noting that *Gran et al. I* studied the hepatitis B polymerase. Tr. 141. However, the authors in *Bogdanos et al.* studied the hepatitis B surface antigen and demonstrated cross-reactivity between at least one hepatitis B surface antigen and myelin protein. Tr. 44, 157-59; Pet. Ex. 45 at 1.[87] Additionally, *Gran et al. II* discussed evidence of molecular mimicry in a patient who developed MS following hepatitis B vaccination. Pet. Ex. 43;[88] Pet. Ex. 42 at 8.[89]

Dr. Sriram's opinion that molecular mimicry between the hepatitis B vaccine and myelin proteins does not occur was rooted in the fact that scientists have not yet been able to conclusively determine an MS-specific autoantibody or prove what causes MS. Tr. 145, 150-51. However, the lack of certainty does not defeat a petitioner's claim in the Vaccine Program. *Knudsen*, 35 F.3d at 548.

As the literature filed in this case confirms, the relationship between MS and the hepatitis B vaccination has been extensively studied for over 30 years and continues to be studied with the theory that a hepatitis B vaccine-induced immune response can lead to demyelination in the CNS. Pet. Ex. 42 at 7;[90] Pet. Ex. 43;[91] Resp. Ex. U.[92] As explained by both experts, MS is a rare event, making it difficult to study. Tr. 38, 66-67, 78, 80-81, 90, 151-52. While there is no definitive answer as to whether the hepatitis B vaccine can cause MS, the Vaccine Program does not operate in absolutes. It is not petitioner's burden to provide unequivocal proof that the hepatitis B vaccine can cause or aggravate MS. Petitioner's burden is that of preponderant evidence by providing a sound and reliable scientific theory. Her theory here has been the working theory of scientists studying hepatitis B vaccine and MS for roughly 30 years. Tr. 140, 151-52; Pet. Ex. 42;[93] Resp. Ex. U.[94]

Therefore, petitioner has provided preponderant evidence to satisfy her burden in proving *Althen* Prong 1/*Loving* Prong 4.

b. *Althen* Prong 2/*Loving* Prong 5: Petitioner Has Provided a Logical Sequence of Cause and Effect Between the Subject Hepatitis A/B Vaccine and Her MS.

[86] Gran, MD, et al., *supra* note 20.
[87] *Id*.
[88] Gran et al., *supra* note 25.
[89] Institute of Medicine 2002, *supra* note 17.
[90] *Id*.
[91] Gran et al., *supra* note 25.
[92] Institute of Medicine 2012, *supra* note 83.
[93] Institute of Medicine 2002, *supra* note 17.
[94] Institute of Medicine 2012, *supra* note 83.

Dr. Tornatore explained that while RRMS has no expected course, the tempo in this case was remarkably rapid. Tr. 84, 87. Petitioner had a normal neurological examination on January 25, 2011, prior to the February 16, 2011 hepatitis A/B vaccination. Tr. 6-7; Pet. Ex. 2 at 155. Her visual acuity was 20/20 in both eyes following conjunctivitis. Tr. 7; Pet. Ex. 2 at 155. She had a "Negative APD." Tr. 7; Pet. Ex. 2 at 155. However, on February 23, 2011, petitioner reported onset of blurry vision five days after vaccination. Tr. 10-11; Pet. Ex. 2 at 151-52. Her visual acuity was then measured as 20/35. Tr. 11-12; Pet. Ex. 2 at 151. She had a distorted Amsler grid, indicative of visual disturbance of either the retinal or optic nerve. Pet. Ex. 2 at 151. Dr. Tornatore opined that this reflected "something acute, a new onset, which goes along with her history." Tr. 14. On March 3, 2011, her vision was 20/40 and APD testing was abnormal with papillary defect and color desaturation. Tr. 16-17; Pet. Ex. 2 at 143-44. ON was suspected. Tr. 17; Pet. Ex. 2 at 144. Petitioner presented to the ER on March 4, 2011 for worsening vision and received IV Solu-Medrol, which is standard practice for ON. Tr. 19; Pet. Ex. 2 at 14-15. A lumbar puncture performed on March 28, 2011 showed only one nucleated white cell, which was important because MS patients have upwards of 40 white blood cells; the presence of only one suggested the acute nature of the inflammation, according to Dr. Tornatore. Tr. 20-21, 24-25; Pet. Ex. 2 at 11. There were also no oligoclonal bands in the CSF, which was significant because if inflammation had been present for some time, the CSF would have shown oligoclonal bands. Tr. 21-25; Pet. Ex. 2 at 12.

The March 3, 2011 brain MRI showed numerous abnormal white matter regions with the distribution of typical demyelinating lesions associated with MS and both enhancing and non-enhancing lesions. Tr. 8-9; Pet. Ex. 2 at 1. The MRI of the optic nerve showed diffuse enlargement and enhancement of the right optic nerve, consistent with acute optic neuritis. Tr. 17-19; Pet. Ex. 2 at 3. Dr. Tornatore explained that the findings could be interpreted in two ways: 1) the non-enhancing lesions were older than three weeks or 2) the lesions developed more recently, but the inflammation was so small that there was no ability for the dye to cross the BBB. Tr. 9, 59. Relying on *Cotton et al.*, Dr. Tornatore noted that all of the large lesions were enhanced on the March 3, 2011 MRI, suggesting that they were less than two to three weeks old. Tr. 159-60. Further, the fact that there were no black holes observed on the MRI is evidence that the lesions were not of long-standing duration. Tr. 161-62.

Dr. Tornatore agreed that petitioner could have had prior lesions that did not cause perceivable symptoms prior to the vaccine. Tr. 22-23. Dr. Tornatore was "very, very convinced that there was an acute inflammatory event triggered by the vaccination and whether that may have been de novo or, otherwise, it was a very significant aggravation of a very low-grade inflammation that had been asymptomatic prior." Tr. 36, 55, 59-60, 68, 87-88. People with bad MS have continuing enhancing lesions; but it is unusual for someone to be fine, then "all of a sudden for the next five years…they start having horrible disease." Tr. 88-89. Based on the rapid progression of her symptoms five days following the subject vaccine, Dr. Tornatore opined that the vaccine caused or significantly aggravated petitioner's MS. Tr. 33-36.

Dr. Tornatore submitted that petitioner's first clinical manifestation of MS was her ON. Tr. 57. In the weeks that followed her initial symptoms, petitioner developed fatigue, which over 50-60% of MS patients have and is thought to be due to immune activation. Tr. 27. Her next MRI on September 27, 2011, showed progressing disease with multiple new enhancing lesions, despite

being treated with disease modifying therapy. She met the criteria for RRMS. Tr. 28-29; Pet. Ex. 2 at 5-6.

Two years after her initial diagnosis of ON, on April 8, 2013, her MRI was consistent with extensive MS. Tr. 33; Pet. Ex. 15 at 11-12. Six years later, petitioner's MS was still not actively suppressed, with her MRIs continuing to show active demyelination. Tr. 35; Pet. Ex. 32 at 9-10. Looking at the totality of petitioner's clinical course and testing, Dr. Tornatore submitted that the inflammation started "just very, very, very close" to when the vaccine was given. Tr. 61. "That's – what's so interesting about this case is that there is a defining event and that the spinal fluid really spoke to something that was new or nascent". Tr. 64.

Dr. Tornatore agreed that there is no known cause for MS, but in rare cases when an inciting event exists, it makes sense that it could be the trigger. Tr. 55. Dr. Tornatore has treated over 4,000 MS patients in over 30 years and never had one that he believed had vaccine-related MS. However, he maintained that this is a very rare occurrence. Tr. 56, 85. He maintained that here, "there really is a trigger that we can point to." Tr. 56-57.

According to Dr. Sriram, petitioner had the classic features of RRMS. He agreed that optic neuritis was the defining event for petitioner's MS, with onset 5 days after her vaccination. Tr. 125, 127-32, 149; Pet. Ex. 2 at 3. However, he believed that, if an MRI had been done prior to vaccination, brain lesions would have been observed. Tr. 149-50. Dr. Sriram submitted the *Brex et al.* article to show that lesions can exist on the brain without symptoms, with 50-70% of those with evidence of brain lesions being asymptomatic. Tr. 136-38; Resp. Ex. LL.[95] Petitioner's March 3, 2011 MRI merely "cemented the diagnosis" of MS, in Dr. Sriram's opinion. Tr. 132.

Dr. Sriram disagreed that petitioner's normal CSF result on March 28, 2011 was an indication that her MS was not longstanding. He submitted that only 50-60% of MS patients have oligoclonal bands in early MS. Tr. 133-34; Pet. Ex. 2 at 12.

Dr. Sriram agreed that petitioner was asymptomatic until five days after receipt of the hepatitis B vaccine, but he thought it "highly unlikely" that the vaccine caused an inflammatory process that triggered those lesions. Tr. 150.

The experts herein seemed to agree more than they disagree. It is undisputed that petitioner had no prior neurological symptoms before she received the subject vaccine. Tr. 28, 107; Pet. Ex. 18 at 15; Pet. Ex. 22 at 2-3; Resp. Ex. Q at 1. It also undisputed that she developed her first clinical manifestation of MS (ON) five days after the vaccine. Tr. 45-46, 128, 130, 149, 163; Pet. Ex. 22 at 1-2; Resp. Ex. A at 1.

Dr. Tornatore posited that petitioner either 1) had pre-existing brain lesions that were significantly aggravated by the vaccine, thus making her then-asymptomatic MS symptomatic, or 2) developed brain lesions as a result of the subject vaccine. Tr. 9, 36, 59. Either way, Dr. Tornatore argued that the rapid progression of petitioner's MS symptoms after vaccination cannot be ignored. Tr. 33, 36, 73, 87. He opined that petitioner was exposed to an antigen in the hepatitis B vaccination, resulting in molecular mimicry and her ultimate diagnosis of RRMS. *See generally* Pet. Ex. 18; Pet. Ex. 22. Dr. Sriram submitted, on the other hand, that the hepatitis B vaccination

[95] Brex, M.D., et al., *supra* note 53.

was unrelated to petitioner's MS because there is insufficient evidence to support a link between the two. Resp. Ex. A at 3; Resp. Ex. V at 1. Additionally, he claimed that the March 3, 2011 MRI showed non-enhancing lesions that were most likely present prior to her receipt of the subject vaccine. Tr. 124; Resp. Ex. Q at 2; Resp. Ex. V at 1.

Although they relied on the same literature to support their respective positions, the experts disagreed on the duration of the lesions seen on petitioner's March 3, 2011 MRI. Dr. Tornatore opined that the lesions were likely 2-3 weeks old, while Dr. Sriram submitted they were anywhere from 6-12 weeks old. Tr. 47, 122-23; Pet. Ex. 41; Resp. Ex. X.[96] Nevertheless, whether petitioner's brain lesions predated the vaccine is not a dispositive issue because petitioner has argued, in the alternative, that her MS was caused by or significantly aggravated by the vaccine. *See* Amended Pet. at 3. Thus, even if the lesions were present before the vaccine, then the hepatitis A/B vaccine significantly aggravated petitioner's then-asymptomatic MS.

Dr. Sriram provided no alternative explanation for the onset and rapid progression of petitioner's MS symptoms following receipt of the hepatitis A/B vaccination other than to say it was not the vaccination because the cause of MS is unknown. Tr. 140, 144, 149-51; Resp. Ex. Q at 2. Dr. Sriram's opinion on this prong seemed to be the same as his opinion on the first: the vaccine did not trigger MS in this case because there is insufficient evidence to support that it can trigger MS at all. For the reasons detailed in the previous section, I do not find Dr. Sriram's argument persuasive.

I agree with Dr. Tornatore that the progression of her symptoms following the vaccine cannot be ignored. Succinctly, petitioner had no symptoms prior to the vaccination. Five days after she received the vaccine, she developed optic neuritis. Shortly thereafter, on March 3, 2011, petitioner underwent an MRI, which showed both enhancing and non-enhancing lesions on her brain and acute inflammation of the optic nerve. Pet. Ex. 18 at 15.

Dr. Tornatore convincingly explained that lesions will remain enhanced for a median of two weeks. Pet. Ex. 41.[97] In this case, that places the beginning of the enhancement after vaccination. Her ON symptoms are consistent with this finding. *See generally* Pet. Ex. 22. Optic neuritis is a common symptom of MS, and the experts agreed that she complained of ON symptoms five days after vaccination. Tr. 45-46, 128, 130, 149, 163; Pet. Ex. 22 at 1-2; Resp. Ex. A at 1. They also both agreed that ON was petitioner's first symptom of her MS. Tr. 45, 49, 107, 128, 130-32, 149; Pet. Ex. 18 at 15; Pet. Ex. 22 at 1; Resp. Ex. A at 3.

On March 28, 2011, petitioner had a lumbar puncture that did not reveal any oligoclonal bands. Pet. Ex. 2 at 12, 37. Although the percentages cited were different, the experts agreed that the overwhelming majority of patients with long-standing MS will have oligoclonal bands. Tr. 22, 70, 74, 133; Pet. Ex. 18 at 15; Pet. Ex. 22 at 2. Notably, Dr. Sriram stated that oligoclonal bands are less frequently seen in patients with early MS. Tr. 133. The fact that petitioner did not yet have oligoclonal bands on March 28, 2011 further supports the notion that the onset of her MS was acute.

[96] Cotton et al., *supra* note 6.
[97] *Id.*

The lumbar puncture additionally showed only one nucleated white blood cell, which was within the normal range. Tr. 20; Pet. Ex. 2 at 11. MS patients typically have upwards of 40 white blood cells. Given that petitioner's MS diagnosis is undisputed, the presence of only one white blood cell is indicative of the acute nature of the inflammation. Tr. 20-21.

Dr. Tornatore explained that petitioner had a rapid immune response to the subject vaccine because her immune system was already primed by the first hepatitis B vaccine. Pet. Ex. 18 at 15. According to Dr. Tornatore, the IOM accepted this as a persuasive theory. Tr. 49. Petitioner received the first hepatitis A/B vaccine on April 26, 2010. Pet. Ex. 7 at 1. Upon receipt of the second vaccine in the series, petitioner had a quick immune response, consistent with an already-primed immune system, and manifested her first MS symptoms shortly thereafter. Tr. 45-46, 128, 130, 149, 163; Pet. Ex. 22 at 1-2; Resp. Ex. A at 1. Notably, Dr. Sriram did not comment on or disagree with Dr. Tornatore's testimony regarding priming. After further progression of her symptoms, petitioner was diagnosed with RRMS. Tr. 29, 32, 116, 126, 133; Pet. Ex. 5 at 77; Resp. Ex. V at 1.

The Federal Circuit in *Capizzano* emphasized the weight to be afforded to the opinions of treating physicians. 440 F.3d at 1326; *see also Andreu*, 569 F.3d at 1375. Although none of petitioner's treating physicians concluded that the hepatitis B vaccine caused or exacerbated her MS, at her disability evaluation performed on September 23, 2011, Dr. Friedrich concluded that it was certainly possible the disease began prior to service. However, Dr. Friedrich noted that there was no way to confirm it, so it is prudent to conclude it developed after she began service. Pet. Ex. 2 at 69-72. In the disability evaluation, the vaccination prior to onset of symptoms was documented. *Id*.

Nevertheless, a causal opinion from a treating physician is not required for a petitioner to prevail in the Vaccine Program. Rather, a petitioner may rely on the opinions of an expert to satisfy their burden. *LaLonde*, 746 F.3d at 1341. For the reasons stated above, Dr. Tornatore provided a persuasive theory linking the subject vaccine to the significant aggravation of MS. Further, Dr. Tornatore convincingly explained how petitioner's medical history following the vaccine was consistent with the proposed theory. Thus, petitioner provided a persuasive opinion that there was a logical sequence of cause and effect between the hepatitis B vaccine and petitioner's MS. Based on the foregoing, petitioner has satisfied *Althen* Prong 2/*Loving* Prong 5.

c. *Althen* Prong 3/*Loving* Prong 6: Petitioner Has Established a Proximate Temporal Relationship Between the Subject Hepatitis A/B Vaccine and the Onset of Her MS.

The prevailing view for the onset of demyelinating diseases following vaccination is that an immune response to an antigen can take anywhere from a few days up to 3-4 weeks. For example, this is recognized on the Vaccine Injury Table as it relates to the onset of GBS within 3-42 days following vaccination. 42 C.F.R. § 100.3(a). There was no disagreement on this issue in this case.

In the Omnibus Proceeding for hepatitis B vaccine-demyelinating injury cases, a 3–60-day timeframe between receipt of hepatitis B vaccine and onset of Guillain-Barre Syndrome,

transverse-myelitis, multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy was found to be medically appropriate. *See Pecorella v. Sec'y of Health & Human Servs.*, No. 04-1781V, 2008 WL 4447607 (Fed. Cl. Spec. Mstr. Sept. 17, 2008); *Stevens v. Sec'y of Health & Human Servs.*, No. 99-594V, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006); *Gilbert v. Sec'y of Health & Human Servs.*, No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006); *Werderitsh v. Sec'y of Health & Human Servs.*, No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006); *Peugh v. Sec'y of Health & Human Servs.*, No. 99-638V, 2007 WL 1531666 (Fed. Cl. Spec. Mstr. May 8, 2007).

Here, petitioner's ON and subsequent MS had an onset five days after she received the second hepatitis A/B vaccination. Thus, petitioner has satisfied *Althen* Prong 3/*Loving* Prong 6.

d. *Loving* Prong 1: Petitioner's Condition Prior to Her Receipt of the Subject Hepatitis A/B Vaccine.

The *Loving* test next requires a determination of petitioner's condition prior to the vaccination she received on February 16, 2011. Review of petitioner's medical records shows that she had no prior history of neurological or visual symptoms. Tr. 28, 107; Pet. Ex. 18 at 15; Pet. Ex. 22 at 2-3; Resp. Ex. Q at 1. Petitioner's physical on January 25, 2011, shortly before her receipt of the subject vaccine, showed petitioner to be neurologically intact with 20/20 vision. She also had a normal APD. Tr. 7; Pet. Ex. 2 at 155-57.

e. *Loving* Prong 2: Petitioner's Current Condition Following Her Receipt of the Subject Hepatitis A/B Vaccine.

The next part of the *Loving* test is to discuss "the person's current condition (or condition following the vaccination if that is also pertinent)." *Loving*, 86 Fed. Cl. at 144. The experts agreed that petitioner's MS onset of ON was five days after vaccination and progressed rather rapidly thereafter. Tr. 29, 32-33, 35, 45-46, 87, 111-12, 128, 130, 149, 163; Pet. Ex. 22 at 1-2; Resp. Ex. A at 1-2. Following vaccination, she presented to the optometrist complaining of persistent vision problems and was reported to have 20/35 and subsequently 20/40 vision. Tr. 16; Pet. Ex. 2 at 143, 151. Thus, not only was her vision worse than her visit on January 25, 2011, but it was actively worsening. Her APD was also abnormal following vaccination. Pet. Ex. 2 at 142-44.

In the months and years that followed her initial MS symptoms, petitioner underwent several MRIs and received treatment for her MS. Yet even in 2019, eight years after the subject vaccine, petitioner's MRI showed active demyelination. Pet. Ex. 32 at 9-10. It is undisputed that petitioner remains gravely affected by her RRMS.

f. *Loving* Prong 3: There was a Significant Aggravation of Petitioner's MS Following Her Receipt of the Subject Hepatitis A/B Vaccine.

The final prong of the *Loving* test is to determine whether there is a "significant aggravation" of petitioner's condition by comparing her condition before vaccination to her condition after vaccination. The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness

accompanied by substantial deterioration in health." § 33(4). Using this definition, the undersigned finds that, based on the facts and circumstances here, petitioner had a significant aggravation of her underlying MS.

Petitioner had no neurological or visual symptoms prior to her receipt of the February 16, 2011 hepatitis A/B vaccination. Tr. 28, 107; Pet. Ex. 18 at 15; Pet. Ex. 22 at 2-3; Resp. Ex. Q at 1. Petitioner had no MRIs performed of the brain or optic nerves prior to March 3, 2011. Thus, there is no way to know for certain whether the non-enhancing lesions seen on the March 3, 2011 MRI are lesions that predated the vaccine or lesions that developed after the vaccine. However, petitioner's condition clearly worsened following the vaccine. Tr. 29, 32-33, 35, 45-46, 87, 111-12, 128, 130, 149, 163; Pet. Ex. 22 at 1-2; Resp. Ex. A at 1-2.

Following the receipt of the February 16, 2011 hepatitis A/B vaccination, petitioner's MS rapidly progressed. Despite treatment, MRIs continued to show inflammatory activity in the brain and spinal cord, suggesting that the disease is still not under control. Tr. 35, 112, 155; Pet. Ex. 25 at 109, 111; *see generally* Pet. Ex. 32. Petitioner was medically discharged from the military and has "experienced a steady decline in [her] abilities" as a result of her MS. *See generally* Pet. Ex. 11. She described her chronic fatigue, limited vision, constant illnesses, and depression due to her MS. *Id*. I find that petitioner's condition following vaccination constitutes a significant aggravation under the statute. Thus, petitioner meets the criteria of *Loving* Prong 3.

g. Alternative Cause

Once a petitioner establishes a prima facie case, the burden of proof shifts to respondent to prove by a preponderance of the evidence that the "illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition." § 13(a)(1)(B); *Walther*, 485 F.3d at 1151. I find that respondent has failed to establish any other cause for the triggering or development of petitioner's MS. Viewing respondent's evidence in its most favorable light, Dr. Sriram opined that the cause of MS is unknown, and thus, unrelated to vaccination. He stated that it was "highly unlikely" that the vaccine caused an inflammatory process that triggered lesions. Tr. 150. Therefore, it was his opinion that the hepatitis B vaccine petitioner received did not play a role in her development of MS. Resp. Ex. A at 5; Resp. Ex. Q at 3; Resp. Ex. V at 1.

Dr. Sriram did not provide an alternative explanation for petitioner's development of ON and RRMS five days after the receipt of the second hepatitis A/B vaccination or for the abrupt and rapid decline in petitioner's condition thereafter. In fact, Dr. Sriram stated that he does not know what caused petitioner's ON or MS. Tr. 150-51.

The Vaccine Act excludes "any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition" from the "factors unrelated" to the vaccine upon which respondent's proof may rest. *See generally* § 13. Respondent's argument that the cause of MS is unknown is insufficient to carry his burden of proving an alternative cause unrelated to vaccination. Thus, because petitioner has carried her burden in establishing a prima facie case of causation, and respondent has failed to establish an alternative cause, petitioner is entitled to compensation.

VIII. Conclusion

Petitioner has proven by preponderant evidence that the hepatitis B vaccination she received on February 16, 2011 significantly aggravated her then-asymptomatic multiple sclerosis. Respondent did not provide an alternative explanation unrelated to the vaccine. Thus, petitioner is entitled to compensation. Accordingly, this matter shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master