# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**
**No. 17-642V**
**Filed: February 1, 2021**
PUBLISHED

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| ELIZABETH DOLES,<br><br>Petitioner,<br>v.<br><br>SECRETARY OF HEALTH AND HUMAN SERVICES,<br><br>Respondent. | Special Master Horner<br><br>Ruling on Entitlement; Ruling on the Written Record; Multiple Sclerosis; Significant Aggravation; Diphtheria acellular Pertussis (Tdap) Vaccine; Polio Vaccine |

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*Catherine Elizabeth Stolar, U.S. Department of Justice, Washington, DC, for respondent.*

## RULING ON ENTITLEMENT[1]

On May 16, 2017, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that she suffered acute disseminated encephalomyelitis ("ADEM") as a result of her receipt of the polio vaccination on April 4, 2016 and/or the tetanus, diphtheria, and pertussis ("Tdap") vaccination on April 22, 2016. (ECF No. 1.) On July 5, 2019, petitioner amended her petition, now alleging that the vaccinations she received in April of 2016 caused her central nervous system ("CNS") demyelination best categorized as multiple sclerosis ("MS"). (ECF No. 44.) Petitioner alleged that her condition was caused, or alternatively significantly aggravated, by her vaccinations. (*Id*. at 2-3.) For the reasons set forth below I conclude that petitioner is entitled to compensation for a significant aggravation of her MS.

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

## I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about 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 proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

*Althen*, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

Generally, respondent bears the burden of demonstrating the presence of any alternative cause by preponderant evidence only if petitioner satisfies her *prima facie* burden. § 300aa-13(a)(1)(B); *Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1150 (Fed. Cir. 2007). Respondent may also present evidence relating to an alternative cause to demonstrate the inadequacy of petitioner's evidence supporting her case in chief, but petitioner does not bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case under *Althen*. *de Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352-53 (Fed. Cir. 2008); *Walther*, 485 F.3d at 1150.

In this case, petitioner has alleged first and foremost that her Tdap and/or polio vaccines caused her to suffer ADEM, MS, or, more generally, central nervous system demyelination. Because these conditions are not listed on the Vaccine Injury Table relative to either the Tdap or polio vaccines, petitioner would need to satisfy the above-described *Althen* test for establishing causation-in-fact to prevail on the basis that her vaccinations initially caused her condition. Significantly, however, respondent argues that petitioner suffered underlying, pre-existing MS that prevents her from demonstrating that her vaccinations initially caused her central nervous system demyelination. (ECF No. 70, p. 23.) This raises an additional question of whether petitioner may have nonetheless experienced any significant aggravation of that condition consistent with her alternative pleading of the claim. (ECF No. 44, pp. 2-3.)

The Vaccine Act defines a significant aggravation as any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness

accompanied by substantial deterioration of health. § 300aa-33(4). Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a pre-existing injury, petitioners must establish the three *Althen* prongs along with three additional factors described in the prior *Loving* case. *See Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013)(applying the six-part *Loving* test.). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

For the reasons discussed below, I conclude that this claim is best addressed under the significant aggravation test articulated in *Loving*.

## II. Procedural History

This case was originally assigned to Special Master Millman. (ECF No. 4.) Upon review of the records filed initially (Exs. 1-12), Special Master Millman raised the issue of a conflict in diagnosis. (ECF No. 9.) Special Master Millman suggested that the medical records favored the diagnosis of multiple sclerosis ("MS") rather than ADEM. (*Id*. at 1.) Additionally, Special Master Millman noted that upon her review of the records, it appears that petitioner's onset of symptoms was June 4, 2016. (*Id*.)

Subsequently, petitioner filed additional records and a Statement of Completion. (ECF Nos. 14-16.) On April 24, 2018, respondent filed his Rule 4(c) report, recommending against compensation. (ECF No. 21.) Respondent indicated that the medical records presented an unclear diagnosis, and even assuming petitioner can establish that she suffered ADEM, petitioner failed to meet her burden in proving causation. (*Id*. at 16-17.)

On May 30, 2018, petitioner filed a letter from her treating physician, Dr. Slavenka Kam-Hansen to support her claim. (ECF No. 23; Ex. 17.) Dr. Kam-Hansen opined that petitioner suffered ADEM. (*Id*.) Respondent indicated that he intended to continue defending the claim. (ECF Nos. 24, 25.) However, petitioner advised an additional report from a different expert would be filed and, on May 24, 2019, petitioner filed a report from Dr. John G. Steel. (ECF No. 34; Ex. 20.) Dr. Steel did not support Dr. Kam-Hansen's ADEM opinion.

This case was reassigned to my docket on June 6, 2019 upon Special Master Millman's retirement. (ECF No. 41.) Respondent requested that petitioner file an amended petition and updated medical records clarifying the nature of the injury in light of Dr. Steel's report opining that petitioner has MS rather than ADEM. (ECF No. 42.) On July 5, 2019, petitioner filed an amended petition alleging that her vaccinations caused her to suffer from "residual effects and complications of CNS demyelination,

including but not limited to: fatigue, significantly heightened temperature sensitivity, pain and neuropathy in her right upper extremity, and the severe emotional and psychological effects of these and other chronic symptoms," noting that Dr. Steel felt the condition was best categorized as MS. (ECF No. 44, p. 2.)

In response, respondent filed a report from neurologist, Dr. Subramaniam Sriram. (ECF No. 52.) On January 31, 2020, petitioner filed a supplemental expert report responding to respondent's expert report. (ECF No. 57.) Thereafter, respondent filed his supplemental expert report from Dr. Sriram on May 14, 2020. (ECF No. 62.) Petitioner then requested that this case be resolved based on the written record. (ECF No. 63.)

On July 29, 2020, petitioner filed a motion for findings of facts and conclusions of law accompanied by a supporting memorandum. (ECF Nos. 67, 68.) Petitioner, in her motion, alleges that the polio and Tdap vaccinations administered on April 4 and 22, 2016 triggered an attack of acute partial transverse myelitis ("APTM"), revealing petitioner's clinically silent MS. (ECF No. 68.) On October 27, 2020, respondent filed a response contending that petitioner had not met her burden of proof and that the case should be dismissed. (ECF No. 70.) Petitioner filed a reply on December 4, 2020. (ECF No. 72.)

Special masters "must determine that the record is comprehensive and fully developed before ruling on the record." *Kreizenbeck v. Sec'y of Health & Human Servs.*, 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs.*, 671 F.3d 1368, 1385 (Fed. Cir. 2012); *Jay v. Sec'y of Health & Human Servs.*, 998 F.2d 979, 983 (Fed. Cir. 1993.)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2). The parties must have a full and fair opportunity to present their case and develop a record sufficient for review. *Id*. In light of all of the above, and upon review of the entire record, I conclude that the parties had a full and fair opportunity to develop the record of this case and that the case is ripe for resolution on the existing record.

## III. Medical History

### a. Pre-Vaccination

Petitioner, 67 at the time of the vaccinations at issue, has a history of Graves' disease. (Ex. 2, p. 51-54.) Petitioner sought treatment at Cambridge Health Alliance for her hypothyroid condition. (Ex. 3.) Her primary care records from 2010 to 2012 indicated she also had a bladder hernia, degenerative joint disease, and underwent a hysterectomy. (*Id*.) She is allergic to penicillin. (*Id*. at 7.) Petitioner has received several vaccinations in the past. (*Id*.) In 2011, petitioner received a physical exam in order to travel to Sri Lanka for work. (*Id*. at 28.) Her exam was normal and she requested several immunizations, denying any allergies to flu vaccine and history of Guillan-Barre syndrome. (*Id*. at 29-30, 33.) In 2015, petitioner had a physical therapy evaluation for ongoing knee and hip pain that worsened over 10 years. (Ex. 4, p. 141-43; Ex. 14, p. 44.)

**b. Vaccination and Initial Treatment**

Petitioner received a polio vaccination on April 4, 2016 and a Tdap vaccination more than two weeks after on April 22, 2016. (Ex. 1.) Petitioner had a mammogram and pap smear on April 4, 2016 (Ex. 5) and an evaluation for colonoscopy on April 8, 2016 (Ex. 7.) Petitioner had a colonoscopy on April 13, 2016. (Ex. 4, p. 116; Ex. 7, p. 6; Ex. 14, p. 28.) On April 21, 2016, petitioner visited Capital Cardiology Associate PA for an evaluation of an abnormal EKG. (Ex. 14, p. 24.) Dr. Bipinpreet Nagra recommended an echocardiogram and stress test due to petitioner's family history. (*Id*.) On April 22, 2016, petitioner visited Lotus Medical Care for "PPD reading,[2] Tetanus shot, forms to be signed." (Ex. 19, p. 3.) Dr. Arkadiy Shraytman noted the visit was for screening of tuberculosis, follow up exam, and immunization. (*Id*. at 5.) Petitioner returned to Lotus Medical Center on May 27, 2016 for "Polio titer" and low back pain and primary generalized osteoarthritis were also noted as problems. (*Id*. at 7.) On June 1, 2016, petitioner visited Lotus Medical again to review her results and occipital neuralgia and iodine-deficiency were noted. (*Id*. at 10-12.)

On June 5, 2016, petitioner sought treatment at Capital Health Regional Medical Center emergency room for right side weakness and numbness, which began two nights prior. (Ex. 2, p. 50-51.) Two hours prior to arriving at the emergency room, petitioner reported experiencing itchiness and redness from scratching along AC joint and right shoulder. (Ex. 8, p. 39.) Petitioner had a consultation for a transient ischemic attack (TIA). (Ex. 8, p. 2.) Petitioner presented with achy pain in her right upper extremity, including her shoulder, neck stiffness, and mild weakness in her right grip. (*Id*.) Petitioner's head CT did not show any acute changes, only chronic lacunar infarctions. (*Id*.) Dr. Rajat Kumar examined petitioner and assessed that she presented with transient right upper extremity achiness and grip weakness. Dr. Kumar indicated that petitioner's CAT scan found lacunar infarcts and therefore, recommended additional imaging. (Ex. 2, pp. 60-61.) Petitioner underwent several imaging studies on June 5, 2016. Her angiography of the neck and head without contrast found no evidence of aneurysmal dilation or significant stenosis. (*Id*. at 36-37, 42-43.) Petitioner's brain MRI without contrast found no acute infarction, intracranial mass or hemorrhage, but did find multiple nonspecific foci of white matter hyperintensity that suggest a clinical diagnosis of a demyelinating disease. (*Id*. at 40.) Petitioner's head CT without contrast also found no signs for acute intracranial hemorrhage, but revealed patchy regions of white matter hypoattenuation that may reflect microvascular ischemic changes, age indeterminate infarcts, and/or demyelinating disease. (*Id*. at 47-48.) Additionally, right maxillary sinus disease was noted. (*Id*. at 48.) Petitioner received steroids and her symptoms improved. (Ex. 8, p. 54.) Petitioner was discharged to

[2] PPD refers to a tuberculin skin test.

rehab and was found to have an acute demyelinating disease with transverse myelitis.[3] (Ex. 8, p. 33. 54.)

The next day, petitioner returned to Capital Health and was admitted. (Ex. 4, p. 43.) Petitioner also saw Dr. Kumar again for a neurology consult for weakness. Dr. Kumar noted white matter lesions in the periventricular region and subcortically that do not demonstrate enhancement, but observed active demyelinating disease in the right lateral cervical area at C3-C4 that did enhance. (Ex. 8, p. 74.) Dr. Kumar assessed petitioner with acute demyelinating CNS disease, noting her presentation was "suggestive of multiple sclerosis." (Ex. 8, pp. 71-76.) Petitioner received a consultation from Dr. Michael S. Beede on June 11, 2016, for "positive ANA, in the context of previous Graves disease, and with new multiple sclerosis." (Ex. 8, p. 64.) Petitioner's brain and cervical MRI were compatible with the diagnosis of MS. (*Id*. at 64, 152.) Dr. Beede indicated that the positive ANA may be either from petitioner's thyroid disease or MS. (*Id*. at 65.)

Petitioner underwent various MR imaging on June 6, 2016. (Ex. 2, pp. 16-28.) An MRI of the thoracic spine with and without contrast revealed overall no abnormal signal or enhancement within the thoracic spinal cord. (*Id*. at 16.) However, certain regions demonstrated enhancement that were indeterminate and there were mild degenerative changes in the thoracic spine. (*Id*. at 16-17.) Additionally, there was a small disc protrusion that caused mild right subarticular zone stenosis. Follow up was recommended. (*Id*. at 17.) The MRI of the lumbar spine with and without contrast showed degenerative changes in the lumbar spine and a possible impingement upon certain nerve roots. Additionally, the MRI findings also suggested an atypical hemangioma and follow up was recommended. (*Id*. at 20-21.) The MRI of the cervical spine with and without contrast found an abnormal signal within the spinal cord involving the right lateral column. (*Id*. at 23-24.) The brain MRI with and without contrast taken on June 6, 2016 was compared with the MRI without contrast taken on the day before. The more recent MRI still showed multiple regions of white matter hyperintensity mostly in the periventricular and subcortical area running perpendicular to the ependymal surface regions; however, the white matter lesions did not demonstrate enhancement. (Ex. 2, pp. 27-28.) She had a chest x-ray that showed bibasilar subsegmental atelectasis and cardiomegaly. (*Id*. at 31.) And petitioner's head CT did not reveal any acute intracranial findings. However, "scattered areas of white matter hypoattenuation are unchanged with corresponding signal abnormality on the preceding brain MRI, most compatible with a demyelinating process. There is no mass effect." (*Id*. at 34.)

Petitioner was discharged to rehab from Capital Health on June 14, 2016 with multiple diagnoses including acute demyelinating CNS disease/multiple sclerosis, acute weakness of the right side. (*Id*. at 50.) During her stay, petitioner was found to have an acute demyelinating disease with TM and was treated with high dosage of steroids.

[3] In fact, the discharge diagnosis was "acute demyelinating CNS disease/multiple sclerosis." (Ex. 8, p. 54.) Only the "hospital course" notation references "acute demyelinating disease with transverse myelitis." (*Id.*)

Petitioner showed drastic improvements but was still weak and therefore needs rehab and a neurological follow up. (*Id*. at 51.)

Petitioner was admitted into St. Lawrence Rehabilitation Center for general debility upon discharge from Capital Health. (Ex. 4, p. 10.) Dr. Madhu Jain, upon review of systems, noted that petitioner reported double vision in the right eye (premorbid). (*Id*.) Upon examination, petitioner was noted with decreased grip strength and overall strength, decreased fine motor control, and decreased balance. Dr. Jain's impression was mild right-side weakness with new onset diagnosis of MS post steroid therapy with continued weakness in right upper and lower extremity. Petitioner was recommended both physical and occupational therapy to address transfers, ambulation, and self-care. (*Id*. at 11.)

On June 23, 2016, petitioner visited Dr. Shukia for a follow up evaluation of her right-sided weakness. (Ex. 2, p. 2.) Petitioner reported that while she was at Capital Health System, she had a brain MRI that showed some white matter changes, but a couple of days after being discharged, she experienced right leg weakness and returned for a C-spine MRI, which showed an enhancing area of abnormal signal. (*Id*. at 3.) Petitioner sought treatment at St. Lawrence Rehab and reported that her strength significantly improved. Dr. Shukia reported that other than a mild limping feeling in the right leg, petitioner seemed to have returned to baseline. Dr. Shukia suggested a full work up including a spinal tap. However, he noted that petitioner did not have any episode of blindness and that "this lesion in the C-spine is also not more than 2 segments of the cervical column." Petitioner also visited Dr. Shukia on July 14, 2016 for a follow up evaluation for history of possibility of demyelinating disease. (Ex. 2, p. 1.) Dr. Shukia noted that petitioner had a "somewhat bloody" spinal tap that tested positive for oligoclonal bands. (*Id*.) Upon physical examination, petitioner presented normal upper and lower extremity strength. Dr. Shukia's impression was that petitioner presented with a demyelinating disease, most likely MS and discussed petitioner's options regarding treatment and medicine during this visit. (*Id*.)

Petitioner had an occupational therapy evaluation and treatment on June 27, 2016 for MS exacerbation. (Ex. 4, p. 43.) Petitioner showed improvements after one month in rehabilitation in upper extremity strength, coordination, and endurance, but had mild deficits in right shoulder strength and fine motor coordination. (Ex. 4, p. 46.)

**c. Subsequent Post-Vaccination History**

On July 6, 2016, petitioner received an initial consultation from Dr. Chitharanjan Rao at the Lawrenceville Neurology Center. (Ex. 4, p. 8.) Dr. Rao's assessment was that petitioner has a history of acute/subacute onset right sided weakness since June 5, 2016 "in the setting of TDP vaccination in early April 2016." (*Id*.) However, the symptoms have nearly resolved and no further episodes, and therefore petitioner is normal from a neurological standpoint notwithstanding the mild sensory loss in her left hand and diffuse hyperreflexia. Dr. Rao diagnosed petitioner with likely ADEM, probably related to her vaccination, but MS is a possibility. (*Id*.) Dr. Rao recommended

continuing physical and occupational therapy and avoiding receiving vaccinations for the season. (*Id*. at 9.)

Petitioner returned to Lotus Medical on July 12, 2016 for a follow up appointment post hospitalization for possible MS. (Ex. 19, p. 12.) Dr. Shraytman ruled out ADEM, but noted MS and low back pain among petitioner's list of problems. (*Id*. at 13-14.)

Aside from seeking treatment from Dr. Rao, petitioner continued visiting Dr. Shukia for her demyelinating disease. (Ex. 4, p. 104; Ex. 14, p. 18.) Dr. Shukia continued to believe that petitioner most likely has MS. (*Id*.) Petitioner had a broken pinky toe and was treated at Champion Orthopedics on August 1, 2016. (Ex. 4, pp. 95-97.) Petitioner underwent physical therapy at St. Lawrence Rehabilitation Center from June 27, 2016 and was discharged on August 10, 2016. (Ex. 6.) Petitioner "progressed very well with therapy [and met] all goals therefore has been discharged with [home exercise program]." (*Id.* at 5.)

A cervical spine MRI performed on August 17, 2016 again showed lesions and enhancement compatible with a demyelinating process related to petitioner's history of MS. (Ex. 4, p. 49-51.) Petitioner received a follow up evaluation for her MS from Dr. Rao on August 19, 2016.[4] (Ex. 4, p. 1; Ex. 14, p. 1.) According to Dr. Rao, petitioner's VEP tests indicated a mild conduction delay involving the right optic nerve but her spinal tap was traumatic and negative for oligoclonal bands.[5] (Ex. 4, p. 1, 33-35, 52.) Petitioner reported paresthesia in her right and left upper extremity, numbness in her left hand, hyperpathia to touch, but believed she was much better with nearly normal gait. (*Id*. at 1.) Upon review of petitioner's MRI imaging, Dr. Rao indicated that the results were consistent with a history of MS and that no new abnormal findings were detected. (*Id*. at 2.)

Petitioner began receiving primary care at Beth Israel Deaconess Medical Center after moving back to Boston from New Jersey in September 2016. (Ex. 11, p. 2.) Petitioner reported that three neurologists had diagnosed her with MS; however, she "saw a neurologist in whom she now has a lot of confidence who diagnosed her as having [ADEM]." (*Id*.) Petitioner reported experiencing continuing weakness and dysesthesias and acute cramping in right upper extremity. (*Id*.) Dr. Harvey Bidwell noted ADEM after polio vaccine and Tdap injection as part of petitioner's history of present illness. (*Id*. at 12.) Dr. Bidwell accepted petitioner's diagnosis of ADEM and referred petitioner for physical and occupational therapy. (*Id*. at 25.) In addition, petitioner saw Simone D. Martell, LCSW for emotional support in coping with a neurological disease diagnosis. (*Id*. at 10-12, 17-21.)

[4] Petitioner additionally had follow-up visits with Dr. Rao on July 28, 2016 August 18, 2016. The exams were similar and Dr. Rao had the same observations/conclusions.

[5] As Special Master Millman previously observed, Dr. Rao incorrectly stated that petitioner did not have oligoclonal bands and seemed unaware that petitioner had abnormal VEP on the right. (ECF No. 9, p. 1.) Dr. Rao concluded that the lesions of her spinal cord were consistent with petitioner's history of MS, yet Dr. Rao concluded that petitioner did not have MS but ADEM. (*Id*.)

On September 20, 2016, petitioner was admitted to the emergency department at Beth Israel Deaconess Medical Central for seizures. (Ex. 10, p. 3.) Petitioner reported a recent diagnosis of ADEM[6] and symptoms of aura and weakness to extremities (right[7] leg arm and leg numbness). (*Id*. at 6, 8.) Petitioner had a neurology consult for right hand and leg spasms. (*Id*. at 27.) Upon examination Dr. Fay Gao found that petitioner had subjective positive sensory symptoms but no objective deficits to all sensory modalities tested. (*Id*. at 30.) Dr. Gao noted that "[w]hile tonic spasm can occur in the setting of recent demyelination, [petitioner] does not have any other significant signs of myelopathy such as weakness, loss of sensation, though her reflexes are somewhat brisk. A superimposed peripheral sensory neuropathy is possible as well." (*Id*. at 30-31.) In addition, since the symptoms were brief and resolved, Dr. Gao noted that petitioner should follow up with her neurologist and thus, no additional head imaging was ordered; however, Dr. Gao recommended blood work up and routine EEG. (*Id*. at 13, 31.) Petitioner was discharged on the same day. (*Id*. at 20, 26.)

On September 27, 2016, petitioner had a neurological consultation with Dr. Slavenka Kam-Hansen for complaints of development of left lower leg burning following vaccinations. (Ex. 15, p. 5.) Toward the end of October in 2016, petitioner returned to the Japanese Acupuncture Center of Independent Practitioners for acupuncture treatment. (Ex. 9, p. 2.) Petitioner experienced "hot spots" in legs, fatigue, and symptoms in her right and left arm. (*Id*. at 3-6.) Petitioner continued seeking weekly treatment throughout 2016 and into January 2017 but remained symptomatic. (*Id*. at 6-7.)

Petitioner returned to Dr. Kam-Hansen seven weeks after her initial consultation on November 14, 2016. (Ex. 15, p. 15.) Dr. Kam-Hansen listed petitioner's neurological problems as presumed ADEM following two vaccinations in April, where the onset of lower leg burning sensation and pressure in right shoulder began in May. (*Id*.) Dr. Kam-Hansen noted that petitioner was initially diagnosed with MS until Dr. Rao diagnosed ADEM instead. Petitioner reported continued burning sensation in her left shin, foot, and hip as well as throbbing, achy, and pins and needles sensation in her right shoulder running down to her fingertips. (*Id*.) Additionally, petitioner reported experiencing focal seizures again. (*Id*.) Dr. Kam-Hansen concluded that petitioner has ADEM rather than MS, but time will give a clearer diagnosis since recovery after ADEM can take months. (*Id*. at 16.) Subsequent imaging was ordered and petitioner returned to see Dr. Kam-Hansen to discuss the results. (*Id*. at 18.) Petitioner's imaging did not show any new lesions and the cervical cord lesion decreased. (*Id*. at 18, 51-54)

On March 23, 2017, petitioner received another physical therapy evaluation for her diffuse body aches, balance issues, and weakness. (Ex. 15, p. 21.) Petitioner reported sensitivity to cold in her right arm and hot spots and weakness in her legs.

[6] Petitioner reported a possible diagnosis of ADEM or MS. (Ex. 10, p. 22.)

[7] In another part of the emergency room records, it was noted that petitioner had left lower extremity numbness. (Ex. 10, p. 11.)

(*Id*.) The evaluation resulted in physical therapy diagnoses including impaired muscle performance and "impaired motor function and sensory integrity associated with non-progressive disorders of the CNS acquired in adolescent or adulthood." (*Id*.) It was noted that petitioner's presentation seems to be a combination of ADEM related impairments combined with deconditioning; however, petitioner had a good prognosis in light of high functionality and general improvement since onset of symptoms. (*Id*. at 25-26.) She continued with therapy.

On August 3, 2017, petitioner visited Dr. Bidwell for a follow up visit. Petitioner reported fatigue, incontinence, and remaining symptoms of burning sensation in her left shin and foot, throbbing, achy, and pins and needle sensation in her right shoulder to her fingertips. (Ex. 50, p. 4.) Dr. Bidwell assessed that petitioner has a history of ADEM following vaccination in April 2016 and still has fatigue, sensory and pain symptoms, and incontinence. (*Id*. at 6.) He added that petitioner's November 2016 imaging did not show any new lesions and the lesions in her spinal cord decreased. (*Id*.) Additionally, petitioner saw Dr. Bidwell for urinary and fecal incontinence worsened by petitioner's ADEM in August 17, 2017. (Ex. 15, p. 48; Ex. 50, p. 8-9.) Thereafter, petitioner had a urogynecology evaluation at Beth Israel Deaconess Medical Center in October 2017. (Ex. 16, p. 9; Ex. 50, p. 12.) Petitioner was diagnosed with Stage II cystocele and urogenital atrophy. (Ex. 50, p. 16.) Dr. Roger Lefevre indicated that "[a]lthough her documented ADEM lesions occur in the C3-C4 distribution, her urinary and fecal incontinence may be due in part to autonomic/neurogenic dysfunction in the setting of ADEM." (Ex. 16, p. 13.)

Petitioner visited the emergency department in late October 2017 due to swelling, pain, and tenderness in her right toes, which was caused by stubbing them against a chair. (Ex. 51, p. 37.) Petitioner had a closed displaced fracture, but otherwise stable and released home. (*Id*. at 39.) Additionally, on November 15, 2017, petitioner presented to Dr. Adam Landsman as a new patient with complaint of pain in her right foot. (*Id*. at 41.) Dr. Landsman did not recommend surgery, but instead for follow up evaluations and repeat radiographs. (*Id*. at 42.) Thereafter, also in November 2017, petitioner returned to Dr. Bidwell reporting that she had a fracture in her toe. (Ex. 50, p. 25.) Otherwise, this visit was similar to petitioner's visit in August with no particular changes to petitioner's neurological symptoms. (*Id*. at 25-28.)

In early 2018, petitioner sought treatment again from Dr. David Baron, whom she last saw in 2012. (Ex. 51, p. 43.) Petitioner reported developing ADEM following polio and Tdap vaccinations and experiencing mild spasms in her left arm. (*Id*.) On March 22, 2018, petitioner went to the emergency department following a mechanical fall and complained of left wrist pain. (*Id*. at 46.) She was diagnosed with a closed nondisplaced fracture in her left hand. (*Id*. at 49.)

During an encounter on August 13, 2018 with Dr. Baron, petitioner reported that her right arm numbness/encephalopathy "has not been as bad recently." (Ex. 51, p. 57.) Dr. Baron accepted ADEM as the primary encounter diagnosis and noted that it was "thought due to vaccine." (*Id*. at 58.) Two months later, during another encounter,

petitioner was minimally symptomatic and stopped taking gabapentin. (*Id*. at 61.) At this visit in October 2018, Dr. Baron assessed petitioner with neuropathic pain generally as the primary encounter diagnosis. (*Id*.)

In March 2019, petitioner returned to Dr. Bidwell for a referral for physical therapy to improve balance and leg strength. (Ex. 50, p. 30.) Additionally, petitioner requested a form to that would allow her to avoid vaccinations. (*Id*.) Aside from Dr. Bidwell, petitioner also sought care at Cambridge Health Alliance. During a visit on March 27, 2019, petitioner indicated that she hasn't had symptoms for the past two years, but started having right arm paresthesia and right shoulder pain over the past few days. (Ex. 51, p. 2; Ex. 53, p. 2.) After consulting with the on-call neurologist and Dr. Kam-Hansen, Dr. Jaeyoung Yang reported that petitioner's neurological exam was normal. (Ex. 51, p. 67.)

In April 2019, petitioner continued seeking urology treatment from Dr. Heidi Rayala. (Ex. 51, p. 7.) Dr. Rayala described petitioner as having a history of ADEM following vaccination in 2016, "which is when her urination problems started." (*Id*.) In October 2019, petitioner visited Cambridge Health Alliance to visit Dr. Baron, her PCP. (Ex. 53, p. 2.) Dr. Baron noted that petitioner was doing well and the plan was to follow up with Dr. Kam-Hansen regarding her neurological symptoms. (*Id*. at 9.)

## IV. Expert Opinions

### a. Petitioner's Experts

#### i. Slavenka Kam-Hansen, M.D.

On May 29, 2018, Dr. Slavenka Kam-Hansen, a treating neurologist, authored a letter indicating that petitioner first sought treatment at the Neurological Clinic of Beth Israel Deaconess Medical Center on September 27, 2016. (Ex. 17.) Dr. Kam-Hansen noted that petitioner's multiple symptoms started a few weeks after being vaccinated for a Peace Corps mission. Dr. Kam-Hansen examined petitioner again on November 14, 2016 and found petitioner suffering from symptoms of pain, sensory changes and fatigue and sensory changes in her left leg. (*Id*. at 1.) Dr. Kam-Hansen characterized petitioner's condition as ADEM, indicating that:

> [T]he fact that there was a temporal relationship between her symptom start and the preceding vaccination, as well as the lack of any prior neurological symptoms which would suggest the presence of MS before June of 2016, means that ADEM was more likely to cause her symptoms. MS affected individuals start having symptoms usually in the 3rd to 4th decennium of their life and [petitioner] did not have any of these-as a matter of fact, she wanted to join the Peace Corps which supports more her being in good physical shape and thus not affected by a chronic disease such as MS prior to her enlisting.

(*Id*.) Additionally, Dr. Kam-Hansen opined that it is highly likely the polio and Tdap vaccinations administered in April of 2016 caused petitioner to develop ADEM. She indicated that petitioner has a history of Graves disease, which increases the risk of other autoimmune conditions and stated that it has been established that vaccination can trigger an autoimmune process that leads to central nervous system demyelination. (*Id*. at 2.) Dr. Kam-Hansen concluded that "further immunization carries a high and unacceptable risk for [petitioner]" based on her view that petitioner's ADEM was caused by the vaccinations petitioner received in April of 2016. (*Id*.)

ii. John G. Steel, M.D., FAAN

Additionally, petitioner retained board-certified neurologist, John G. Steel to support her claim. Dr. Steel received his medical degree from University of North Carolina School of Medicine in 1977 and completed his neurology residency from the University of California, San Francisco in 1981. (Ex. 20, p. 1.) Dr. Steel worked as clinical faculty for neurology with East Carolina School of Medicine for about 15 years and then practiced in a multispecialty group in New Bern, North Carolina until his retirement in 2017. (*Id*.) However, he retained an active license and continued doing medical legal consulting, including providing prior testimony in the Vaccine Program. (*Id*.)

Dr. Steel opined that petitioner "experienced an attack of focal myelitis (inflammation of the spinal cord), caused by neuroimmune activation from receiving two vaccinations in close proximity." (Ex. 20, p. 3.) Specifically, Dr. Steel indicated that the vaccinations "unmasked" the underlying, asymptomatic MS or radiographically isolated syndrome ("RIS"), referring to a common phenomenon where people with no symptoms or abnormalities on neurological examination who have lesions typical for MS on MRI scans. (*Id*.) It is Dr. Steel's opinion that petitioner meets the current diagnostic criteria for MS. He explained that the former diagnostic criteria required documentation of multiple neurological attacks in time and space throughout a patient's life, whereas currently, the presence of biomarkers can substitute for clinical evidence events as diagnostic criteria. (*Id*.)

Dr. Steel explained that MS is the most common inflammatory immune-mediated CNS demyelinating disease amongst others including ADEM, transverse myelitis ("TM"), neuromyelitis optica ("NMO"), and focal myelitis. (*Id*. at 3.) These disorders share common histopathological findings on microscopic study of damaged tissues and brain magnetic imaging. (*Id*. at 4.) He further explained that "the ability of MRI to distinguish these disorders by their characteristic appearance is high when the disease is classic, but poor when the attacks are mild or very early in the course of the disease." (*Id*.) However, these disorders differ in epidemiology and clinical factors including speed of onset, diversity of symptoms, severity of attacks, outcome, and prognosis. (*Id*.) Relevant to this case, MS is an autoimmune disorder of the CNS where the immune system is overly active and erroneously targets normal body tissue, causing suppression of regulatory cells and an abnormality of the homeostasis of immune regulation in the CNS. (*Id*.)

Relying on epidemiological evidence and clinical experience, Dr. Steel stated that vaccinations combined with other non-specific immunogenic stresses may trigger an immune-mediated attack of demyelination in persons who are susceptible for genetic or other reasons. (*Id*. at 4.) Moreover, "[t]he dissemination of MS clinical events in time means that relating onset of symptoms to specific immune challenges is difficult, and it is likely that triggering of clinically significant MS by vaccine is underreported for this reason." (*Id*.) Because vaccines stimulate a heightened immune reaction response, they may have unintended effects of activating the immune system in the CNS in susceptible persons who are already undergoing an autoimmune process. (*Id*. at 5.) Dr. Steel indicated that mechanisms may include molecular mimicry, epitope spreading, bystander activation, T-helper cell activation, and cytokine induction. A case may involve multiple mechanisms; however, he further described the theory of molecular mimicry relative to vaccinations, explaining "that antibodies formed in response to the vaccine may attack myelin related epitopes if these epitopes are like the antigens in their chemical and physical structure." (*Id*.) Additionally, there is convincing evidence linking reported TM following various vaccinations including measles and rubella, combined diphtheria, tetanus, and polio, and hepatitis B. (*Id*. at 4.) Based on evidence that vaccinations can trigger single attacks of TM, ADEM, optic neuritis, and spinal myelitis, Dr. Steel opined that a vaccine can trigger attacks in patients with subclinical MS. (*Id*. at 5.)

Specifically, Dr. Steel opined that petitioner is "a person with an undiagnosed susceptibility (i.e., clinically silent MS) who developed an attack of focal spinal myelitis after immunization." (*Id*. at 5.) Dr. Steel found that petitioner's MRI scans showed silent lesions that are typical of MS patients, that her cerebrospinal fluid ("CSF") showed presence of oligoclonal bands that indicates on-going production of immunoproteins within the CNS compartment, and that she had abnormal visual evoked responses in the right optic nerve, all consistent with a diagnosis of MS. (*Id*. at 3.) Of note, Dr. Steel stated that oligoclonal bands are present in patients with ADEM, but not seen in isolated attacks of transverse myelitis ("TM") or neuromyelitis optica ("NMO") and that optic neuropathy may be seen in MS, NMO, ADEM, but not TM. (*Id*.) Therefore, Dr. Steel opined that petitioner experienced an attack of spinal myelitis due to immune stimulation from receiving two vaccinations in close temporal proximity and that her underlying, subclinical MS was unmasked by the vaccines. (*Id*. at 5.)

In his supplemental report responding to respondent's expert, Dr. Steel agreed that petitioner has MS, not ADEM, and that petitioner's polio and Tdap vaccinations did not cause her MS. (Ex. 54, p. 1.) Rather, Dr. Steel reiterated that he opined a causal relationship between vaccines and myelitis only and that the vaccines at issue did in fact contribute to petitioner's attack of TM, which revealed petitioner's clinically silent MS. (*Id*.) He further explained that "[t]he family of immune-mediated inflammatory demyelinating disorders exists along a spectrum of severity ranging from limited, highly focal involvement of the central nervous system (optic neuritis, segmental myelitis, Transverse Myelitis) to multifocal involvement with potentially devastating outcomes (Multiple Sclerosis, Acute Demyelinating Encephalomyelitis, Neuromyelitis Optica)." (*Id*.

at 2.) Along this spectrum, the disorders share in common many features including the activation of the immune system to attack normal constituents and differ in spatial and temporal aspects and prognosis. Thus, "[c]ausation is likely multifactorial, with contributing factors including genetic predisposition, environment, nutritional status, comorbidities, and exposure to various triggers." (*Id*.)

He further explained TM in detail and, relying on the Transverse Myelitis Consortium Working Group's published diagnostic criteria, indicated that petitioner met "all the inclusion criteria and exclusion criteria except that her symptoms and signs were unilateral." Dr. Steel concluded that petitioner had an attack of Acute Partial Transverse Myelitis (APTM), which is defined as an idiopathic inflammation of the spinal cord causing asymmetric or mild loss of function due to a lesion that is less than the full transverse anatomy of the spinal cord. (*Id*. at 3 citing Thomas F. Scott, *Nosology of Idiopathic Transverse Myelitis Syndromes*, 115 ACTA NEUROL SCAND 371 (2007) (Ex. 65).) Additionally, Dr. Steel noted that acute partial myelitis is strongly associated with MS. (*Id*.) Dr. Steel then explained that vaccines can trigger TM, pointing to various studies and reports. In particular, Dr. Steel discussed a Kaiser-Permanente study that identified 780 incident cases of CNS acute demyelinating syndromes following vaccinations. The study analyzed the risks of suffering an acute demyelinating syndrome following vaccination and found that among the identified cases, the most common detected disorder was MS. (*Id*. at 5 citing Annette Langer-Gould et al., *Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases*, 71 JAMA NEUROL 1506 (2014) (Ex. 63).) The study concluded that the observations of short-term increase in risk after vaccination in younger patients suggest that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. (*Id*.) Thus, Dr. Steel opined that "it is reasonable to consider that at-risk individuals, such as [petitioner], are more likely to develop complications, [such as a CNS acute demyelinating syndrome,] following vaccination." (*Id*. at 6.)

In this case, considering petitioner's pre-existing autoimmune disorder and clinically silent MS, Dr. Steel opined that petitioner experienced an attack of APTM, a neurological impairment due to the spinal cord lesion, that was most likely triggered by the vaccinations she received in April of 2016. (*Id*. at 7.) Petitioner's onset of pain in the right arm and shoulder, associated with neck stiffness and weakness of her right grip, her progression of right-leg weakness, and her imaging studies including her MRI and CSF, are all consistent with a diagnosis of MS. (*Id*. at 2.)

**b. Respondent's Expert, Subramaniam Sriram, M.B.B.S**

In response, respondent retained Dr. Subramaniam Sriram to defend this case. Dr. Sriram currently holds a teaching position as a professor in neurology and microbiology immunology. (Ex. A.) Additionally, Dr. Sriram is the director of the MS Clinic at Vanderbilt Medical Center, where he cares for over 1000 MS patients. He is board-certified in internal medicine and neurology and authored many publications on MS. (*Id*. at 1.)

Dr. Sriram agreed with Dr. Steel that petitioner has MS and that she met the necessary McDonald criteria for dissemination in space and time to warrant such diagnosis. (Ex. A, p. 7.) Dr. Sriram explained that in some MS patients, there are silent lesions, described as extensive lesions seen radiologically in other parts of the central nervous system predominantly in the white matter of the periventricular regions but do not cause clinical symptoms. He concluded that "[although petitioner] did not have a clinical event before her admission on 6/5/16, other than a prior history of burning sensation in the left leg, the MRI brain lesions in the left frontal, left occipital and right deep white matter suggest otherwise and indicate prior subclinical involvement." (*Id*. at 8.)

Generally, MS is caused by an autoimmune response, but there is a lack of supporting evidence in identifying the specific autoantigen. However, the current evidence indicates that MS is mediated by T lymphocytes, which target the white matter of the CNS, and ongoing inflammatory response in the CNS results in demyelinating lesions in the myelin of the CNS. Patients with MS can have neurological deficits pertaining to the optic nerves, brainstem, or spinal cord and demyelination in the spinal cord may lead to weakness of the arm and legs. (*Id*. at 7, 8-9.) Dr. Sriram stated however that "[t]he prevailing opinion among scientists and the medical community is that there is no causal connection between vaccines and the development of acute clinical worsening, often referred to as a relapses." (*Id*. at 9.) Specifically, studies have failed to show that vaccines initiated and/or propagated clinical worsening and even further that some studies show a decreased risk of developing MS in individuals who received vaccinations. (*Id*. 9-10.)

Dr. Sriram responded to Dr. Kam-Hansen's letter, opining that petitioner had ADEM. Because ADEM is considered to be a monophasic inflammatory disorder that manifests usually in encephalopathy, the absence of encephalopathy excludes a diagnosis of ADEM. (*Id*. at 11.) Upon review of the record and considering petitioner's onset, symptoms, and MRI findings, Dr. Sriram concluded that petitioner did not meet the criteria for ADEM. (*Id*. at 11-12.) Additionally, ADEM is more common in children and despite Dr. Kam-Hansen's reference to petitioner's age as exclusive of MS, Dr. Sriram, instead weighed petitioner's age as against a diagnosis of ADEM. (*Id*. at 13.)

In response to Dr. Steel's first report, Dr. Sriram emphasized that there is no evidence that vaccinations are likely to trigger relapses and that the clinical evidence Dr. Steel presented does not pertain to MS and/or involves vaccinations that are not relevant to this case. (*Id.* at 14-15.) Additionally, Dr. Sriram opined that "[t]he prevailing opinion does not support the view that vaccines, even when given in 'close temporal proximity,' in any way 'trigger' onset or relapses in patients with MS, including individuals with previously clinically silent MS." (*Id*. at 15.) In fact, he opined that, in light of how well-studied MS is, the relationship between the vaccinations at issue and the occurrence of a relapse is coincidental and not causal. (*Id*.) Therefore, Dr. Sriram concluded that the receipt of the polio and Tdap vaccines did not play a role in petitioner's development of a clinical relapse of MS. He stated that "[o]ther than offering

a temporal relationship between [petitioner's] receipt of the Tdap and polio vaccines and the development of clinical and new MRI lesions, Dr. Steel does not provide a biological basis on which vaccines can cause worsening of MS." (*Id*. at 16.)

Dr. Sriram also provided a supplemental report addressing Dr. Steel's second report. (Ex. O.) He explained that MS is a chronic demyelinating disorder that requires evidence of lesions which are disseminated in space and time and clinically; and may present symptoms of neurological deficits pertaining to the optic nerves, brainstem, or spinal cord. He further indicated that "[t]he clinical picture of incomplete transverse myelitis is the most common feature of the myelitic syndrome of MS and fits the clinical finding seen in [petitioner]." (*Id*. at 1.) However, Dr. Sriram stated that Dr. Steel's theory, that petitioner has clinically silent MS that was unmasked after a TM attack, was an attempt to "re-define the myelitic syndrome that is a characteristic of MS as a separate disease entity with a different etiology." (*Id*.) Although the diagnosis of MS is not in dispute, Dr. Sriram explained that Dr. Steel was trying to fault petitioner's myelitis as caused by the vaccine rather than recognizing the myelitis as part petitioner's MS syndrome. (*Id*. at 2.)

Dr. Sriram addressed the medical literature cited by Dr. Steel to support his theory and highlighted several points in rebuttal including examining the paper filed as Exhibit 68 which stated that patients with MRI abnormalities consistent with MS cannot be diagnosed with idiopathic or primary TM. (*Id*. at 2 (citing Transverse Myelitis Consortium Working Group, *Proposed Diagnostic Criteria and Nosology of Acute Transverse Myelitis*, 59 NEUROLOGY 499 (2002) (Ex. 68).) He also opined that "the initial presentation of an inflammatory demyelinating condition like TM becomes a feature of MS once the MS diagnosis is made; it does not remain a separate disease for which there is no clear etiology," citing to his prior reference, the Krupp et al. paper. (*Id*. at 3 (citing Ex. L, pp. 1-3.) Additionally, Dr. Sriram rebutted the possibility of vaccines triggering TM, noting that the case reports cited by Dr. Steel did not include any cases of TM in a patient with MS. (*Id*. at 4.) And specifically, Dr. Sriram criticized the Frohman and Wingerchuk paper, stating that they "cannot simultaneously claim that vaccines cause transverse myelitis in patients with underlying MS and at the same time draw a line between postvaccination transverse myelitis and MS-associated transverse myelitis." (*Id*. at 4-5 (citing Elliot M. Frohman & Dean M. Wingerchuk, *Transverse Myelitis*, 363 N. ENGL J. MED 546 (2010) (Ex. 39).) Overall, Dr. Sriram insisted that the references Dr. Steel cited in his reports failed to provide a credible medical connection between TM as seen in the context of MS and vaccination. (*Id*. at 3-6.)

In summary, Dr. Sriram opined that "[t]here is nothing in the clinical history, MRI findings or the course of disease to suggest that the transverse myelitis is anything other tha[n] what is seen in relapsing remitting MS." (*Id*. at 6.) Therefore, he opined that the vaccinations played no role in the development of petitioner's myelitic symptoms, which were a manifestation of petitioner's underlying MS. (*Id*. at 7.)

## V. Analysis

### a. Diagnosis

"The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the [petitioner]'s injury.'" *Andreu v. Sec'y of Health & Human Servs*., 569 F.3d 1367, 1382 (Fed. Cir. 2009) (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994)). "Although the Vaccine Act does not require absolute precision, it does require the petitioner to establish an injury – the Act specifically creates a claim for compensation for 'vaccine-related injury or death.'" *Stillwell v. Sec'y of Health & Human Servs*., 118 Fed. Cl. 47, 56 (2014) (quoting 42.U.S.C. § 300aa-11(c)). Accordingly, the Federal Circuit has concluded that it is "appropriate for the special master to first determine what injury, if any, [is] supported by the evidence presented in the record before applying the *Althen* test to determine causation." *Lombardi v. Sec'y of Health & Human Servs*., 656 F.3d 1343, 1351-53 (Fed. Cir. 2011).

As a threshold matter, there has been some indication in this case, both in the medical records and in Dr. Kam-Hansen's written opinion, that petitioner's correct diagnosis is ADEM. (Ex. 4, p. 9; Ex. 11, p. 25; Ex. 15, p. 16; Ex. 17, p. 1.) However, Drs. Steel and Sriram, who have each offered multiple reports and discussed their conclusions at greater length, have both concluded that petitioner's ultimate diagnosis is MS. (Ex. 20, p. 3; Ex. 54, p. 1; Ex. A.) This is based not only on their expertise, but also on their review of the complete medical records. Dr. Kam-Hansen, though a treating physician, was less persuasive. In particular, she stressed petitioner's pre-vaccination state of health without addressing the radiological evidence of lesions, discussed further below, that seem to evidence dissemination in time and space (i.e. non-enhancing lesions present in the brain MRI and an enhancing lesion in the cervical spine MRI). (Alan J. Thompson et al., *Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria*, 17 LANCER NERUOL 162, 168 (2018) (Ex. C, p. 7 (Panel 5)).) In any event, Dr. Kam-Hansen's opinion is not shared among all of petitioner's treating physicians, who were split as to whether MS or ADEM was petitioner's correct diagnosis. Moreover, on this record, the relevant literature suggests that while MS may initially be mistaken for ADEM in the short-term, there is not preponderant evidence that ADEM itself evolves into MS. (Nathan P. Young, Brian G. Weinshenker & Claudia F. Lucchinetti, *Acute Disseminated Encephalomyelitis: Current Understanding and Controversies*, 28 SEMIN NEUROL 84 (2008) (Ex. 33.) Accordingly, I will address the causation-in-fact analysis in this case in the context of MS rather than ADEM. *Accord Samuels v. Sec'y of Health & Human Servs.*, No. 17-071V, 2020 WL 2954953 (Fed. Cl. Spec. Mstr. May 1, 2020) (explaining that "Dr. Gelfand persuasively established that there are meaningful clinical and diagnostic differences between ADEM and CIS. Even if ADEM is a type of CNS demyelinating injury, and even if it can constitute an initial MS 'flare,' from a medical/scientific standpoint it is *better* understood as a narrower condition in most cases than Dr. Steinman allowed, with symptoms specific to it that are distinguishable from a first MS presentation.").

### b. Factors Relevant to a Significant Aggravation Analysis

Having concluded that petitioner more likely experienced MS rather than ADEM, the next question to be resolved is the clinical course of petitioner's MS. An examination of petitioner's clinical history under the first three prongs of the above-discussed *Loving* test show this case to be one of significant aggravation of petitioner's pre-existing MS rather than including any separate attack of TM as argued by petitioner.

i. Condition before and after vaccination (*Loving* prongs one and two)

Petitioner's pre-vaccination medical records contain no significant evidence of any outward clinical signs or symptoms of MS or any other central nervous system demyelinating condition prior to her vaccination. However, both Dr. Steel and Dr. Sririam agree that petitioner's post-vaccination MRI study of June 5, 2016 revealed non-enhancing lesions that suggest she had pre-existing, subclinical MS prior to her vaccination. (Ex. 20, pp. 3-4; Ex. A, pp. 7-8.) Specifically, Dr. Steel characterized petitioner's MRI as revealing "lesions in the brain consistent with MS, likely preexistent, likely old, and clinically silent" and opined that this pre-existing MS represented an underlying susceptibility. (Ex. 54, p. 6.) Accordingly, in light of these expert opinions, the weight of evidence favors a finding that petitioner had pre-existing clinically silent MS.[8]

Additionally, regardless of ultimate diagnosis, it is undisputed that petitioner experienced an attack of CNS demyelination less than two months following the vaccinations at issue in this case. (Ex. 2, p. 51.) This is evidenced both by petitioner's first outward clinical manifestation of symptoms and also by objective imaging. (*Id*.) It is also undisputed by the retained experts that petitioner was ultimately correctly diagnosed with MS by at least some of her physicians. (Ex. 2, pp. 2, 50; Ex. 14, p. 18; Ex. 20, p. 3; Ex. 54, p. 3; Ex. A, p. 8; Ex. O, p. 6; ECF No. 70, p. 12.) The question of whether that initial attack of CNS demyelination constitutes a manifestation of

[8] Prior cases in this program have discussed an article by Cotton, et al, which has not been filed into the record of this case. That article suggests that lesions enhance for a median duration of two weeks. *See, e.g. W.C. v. Sec'y of Health & Human Servs.,* No. 07-456V, 2011 WL 4537877 (Fed. Cl. Feb. 22, 2011), *aff'd,* 100 Fed. Cl. 440 (2011), *aff'd,* 704 F.3d 1352 (Fed. Cir. 2013). Based on the timeline of petitioner's treatment, this would suggest that the presence of non-enhancing lesions may not in itself be dispositive of whether petitioner's MS pre-dated her vaccinations. However, Dr. Sriram opined that petitioner's non-enhancing lesions also included so called "black holes," non-enhancing lesions that remain hypointense on T1 imaging. (Ex. A, p. 8.) Dr. Sriram appears to offer a professional judgment that this type of lesion would necessarily be "old" and Dr. Steel has not challenged that judgment on petitioner's behalf. In fact, he agreed that petitioner likely had preexisting MS that he opined left her susceptible to a vaccine injury. (Ex. 20, p. 5; Ex. 54, p. 6.) An additional factor is that the experts find significance in the fact that petitioner had both enhancing and non-enhancing lesions at the time of her initial MRI, which contributed to their assessment that the lesions represented dissemination in time. In sum, both parties have presented expert opinion that petitioner's MS predated her vaccinations and, especially given the lack of dispute, I accept their shared professional judgment based on the record of this specific case. However, it does not necessarily appear that this result would follow in all cases based merely on the presence of non-enhancing lesions.

petitioner's overall course of MS, as respondent contends, or a separate attack of TM, as petitioner contends, is addressed under *Loving* prong three, below.

ii. Significant aggravation (*Loving* prong three)

Contrary to petitioner's assertion, it appears that petitioner's clinical history is more consistent with a significant aggravation of her underlying MS rather than an isolated attack of TM distinct from her overall clinical course of MS. Dr. Steel's assertion of a separate attack of TM does not appear on this record to be consistent with the way in which the medical community understands these conditions. For example, petitioner has filed literature broadly cautioning that idiopathic or primary TM should be distinguished from disease-associated TM, suggesting that "[i]dentification of etiologies may suggest medical treatment, whereas no clearly established medical treatment currently exists for idiopathic ATM." (Transverse Myelitis Consortium Working Group, *Proposed Diagnostic Criteria and Nosology of Acute Transverse Myelitis*, 59 NEUROLOGY 499 (2002) (Ex. 68, p. 1).) Moreover, Dr. Sriram stressed that MS is an exclusionary factor in the diagnosis of TM under the prevailing diagnostic criteria. (Ex. O, pp. 2-3.)

Dr. Steel suggested that it is not sufficient to rely on the Working Group diagnostic criteria for acute TM generally. (Ex. 54, p. 3.) Instead, Dr. Steel suggested that subsequent literature distinguishes between idiopathic TM, acute complete TM ("ACTM"), and acute partial ("APTM"). Under this revised framework, only idiopathic TM requires exclusion of MS. (Thomas F. Scott, *Nosology of Idiopathic Transverse Myelitis Syndromes*, 115 ACTA NEUROL SCAND 371 (2007) (Ex. 65, p. 3 (Table 1)).) Dr. Steel contends that petitioner's case is consistent with the latter APTM. (*Id*.) Critically, however, Dr. Steel acknowledges that APTM, in contrast to ACTM, "is strongly associated with multiple sclerosis, either as an initial presenting disease or as part of the ongoing relapsing-remitting course of MS." (*Id*.) Moreover, the authors explain that:

> Once the specific causes (secondary transverse myelitis) have been ruled out by an initial workup, including probable or definite MS in patients presenting with classic cerebral lesions identified on MRI, the majority of cases with either ACTM or APTM will remain idiopathic. However, a minority of patients initially designated as idiopathic will eventually achieve a diagnosis of a more specific disease state (secondary transverse myelitis). We consider a patient with a syndrome of acute myelitis to be 'as of yet idiopathic cause.' This patient needs to be monitored over time to determine whether this syndrome will eventually be incorporated within a diagnosis of more specific disease (e.g. Devic's syndrome, systemic lupus erythematosus, sarcoidosis). When patients present with APTM and cerebral MRI showing lesions typical of MS, the transition rate to [clinically definite] MS is known to be quite high, in the range of 80-90% within a few years.

(Scott, *supra*, at Ex. 65, p. 5.) Thus, contrary to Dr. Steel's opinion, even this more nuanced understanding of acute TM still does not suggest that an APTM attack is generally accepted as having a distinct etiology when presenting in the context of MS. In fact, the literature that Dr. Steel cited for the specific proposition that immunization may trigger attacks of myelitis in the context of underlying disease (Frohman and Wingerchuk), specifically limits postvaccination TM to longitudinally extensive TM rather than partial TM, the latter of which, consistent with the above, is associated instead with a high risk of MS. (Elliot M. Frohman & Dean M. Wingerchuk, *Transverse Myelitis*, 363 N. ENGL. J. MED 564 (2010) (Ex. 39, p. 3 (chart)).)

Significantly, Dr. Steel also acknowledged that petitioner's overall presentation around the time her symptoms first manifested is more consistent with ongoing MS than with an isolated attack of transverse myelitis. (Ex. 20, p. 3.) Dr. Steel opined that petitioner's spinal lesion is distinct from complete transverse myelitis, because it did not cross the midline of the spinal cord. (*Id*.) He also opined that the presence of oligoclonal bands and optic neuropathy distinguish petitioner's condition from transverse myelitis generally. (*Id*.) Further, there is agreement that petitioner's presentation at the time of her clinical attack evidenced dissemination in time and space, a key diagnostic consideration for MS that is not consistent with an isolated attack. (Ex. 20, p. 3; Ex. A, pp. 7-8; *see also* Thompson et al., *supra*, at Ex. C.) Dr. Steel explained that petitioner's spinal lesion, though typical of MS, is not itself diagnostic. (Ex. 20, p. 3.) However, he agreed that the presence of oligoclonal bands in petitioner's cerebral spinal fluid suggested dissemination in time. (*Id*.) Dr. Steel further indicated that petitioner's abnormal visual evoked responses in the right optic nerve evidenced dissemination in space. (*Id*.) Additionally, although he stressed that petitioner's outward clinical symptoms began post-vaccination, her MRI "revealed lesions in the brain consistent with MS, likely preexistent, likely old, and clinically silent." (Ex. 54, p. 6.)

This assessment of petitioner's own clinical presentation leaves Dr. Steel's opinion even further at odds with this reliance on Frohman and Wingerchuk. That literature includes a diagnostic flow chart that specifically indicates that findings of demyelination on brain MRI, oligoclonal bands, and abnormal visual evoked response should lead to the conclusion of a high risk of MS rather than TM. (Frohman & Wingerchuck, *supra*, at Ex. 39, p. 3.) Under this framework, only the absence of all of these findings would allow for a reconsideration of the clinical history that could potentially lead to a diagnosis of idiopathic, postinfectious, or postvaccination TM. (*Id*.) In fact, respondent argued that "if Dr. Steel had employed the methodology outlined by Frohman and Wingerchuk, he would have concluded that petitioner's 'focal myelitis' or APTM was caused by her underlying MS, not her preceding vaccinations." (ECF No. 70, p. 23.) This is also consistent with the way in which these conditions have been understood in prior program cases. For example, in *Pek v. Secretary of Health & Human Services*, the special master noted a distinction between acute demyelinating injuries such as transverse myelitis and chronic, relapsing demyelinating injuries such as multiple sclerosis. 2020 WL1062959 (Fed. Cl. Spec. Mstr. Jan. 31, 2020). He described a theory of acute injury evolving into a chronic injury as conceivable though yet to be seen.

For all the reasons discussed above, I conclude that it is more likely than not that petitioner's post-vaccination symptoms were a part of the overall clinical course of her pre-existing MS rather than a separate attack of TM. Moreover, consistent with the Vaccine Act's definition of significant aggravation, this constitutes a change for the worse in petitioner's MS, resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 300aa-33(4). This leaves only the question of whether that significant aggravation was vaccine related.

**c. Causation-in-Fact Analysis**

i. Medical theory causally connecting the vaccination and injury (*Althen* prong one/*Loving* prong four)

Petitioner's burden under the first *Althen* prong/fourth *Loving* prong is to provide, by preponderant evidence, "a medical theory causally connecting the vaccination and the injury." *Althen,* 418 F.3d at 1278. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Human & Health Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Moreover, scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, to satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548; *Boatmon*, 941 F.3d at 1359.

Although Dr. Steel focused in significant part on TM, there is also little dispute on this record as to the autoimmune or immune-mediated nature of MS and the fact that clinical attacks in MS can be associated with immune insults.[9] Dr. Sriram indicated that the "cause of MS is thought to be autoimmune in nature although supportive evidence such as the identification of an auto-antigen is lacking." (Ex. A, p. 8.) However, he explained that the prevailing opinion is that MS is mediated by T lymphocytes that create an "ongoing inflammatory response in the central nervous system, [which] results in the development of lesions in the white matter and in particular the myelin membranes of the central nervous system," and this demyelination causes clinical disability such as weakness of the arms and legs, as is the case with petitioner. (*Id*.) Additionally, Dr. Steel explained that MS can be conceived as a disorder of immune regulation involving the balance between regulatory T-cells and dendritic cells. (Ex. 20, p. 4.) Dr. Steel opined that vaccines can create a heightened immune response and in

[9] To be clear, Dr. Sriram does not agree that vaccines trigger clinical attacks of MS. However, he did indicate that "[t]he current opinion on the development of MS is based on the assumption that the inflammatory response and the attendant demyelination is due to an autoimmune process." (Ex. A, p. 9.) That an autoimmune process would have an external trigger is not necessarily controversial. In that regard, in specific response to Dr. Steel's assertion that immunogenic stressors may trigger an immune-mediated attack of CNS demyelination, Dr. Sriram focused exclusively on whether vaccines could be such a trigger and did not dispute the broader assertion that CNS demyelination can be related to immunogenic stressors. (Ex. A, pp. 13-15.)

turn the "antibodies formed in response to the vaccine may attack myelin related epitopes if these epitopes are likely the antigens in their chemical and physical structure." (*Id*. at 5.) In light of the background provided by both experts, Dr. Steel is persuasive in opining that for the entire family of immune-related demyelinating disorders, including MS, "[c]ausation is likely multifactorial, with contributing factors including genetic predisposition, environment, nutritional status, comorbidities, and exposure to various triggers." (Ex. 54, p. 2.)

In that context, the record of this case contains one especially relevant and persuasive study related to significant aggravation of MS. (Annette Langer-Gould et al., *Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases*, 71 JAMA NEUROLOGY 1506 (2014) (Ex. 62)[10].) In 2014 a nested case-controlled study was conducted among Kaiser Permanente patients in southern California. A study population of 780 incident cases of central nervous system acquired demyelinating syndromes ("CNS ADS"), including MS, were identified along with a control population of 3,885. Although the study found no long-term association between vaccination and MS, it did uncover a statistically significant increased risk of onset of CNS ADS within 30 days of any vaccination among individuals under 50 years of age. Although the study focused on HPV and Hepatitis B vaccinations, the study examined a wide range of vaccinations, including both polio and tetanus vaccinations, and concluded that the increased risk followed all vaccinations.

The study authors explained in light of their overall findings that "this association disappeared after 30 days, suggesting that, at most, vaccines are redundant enhancers of preexisting autoimmunity." (*Id*. at 5.) More specifically, the authors observed that

> [t]his argues against causality because the risk in the vaccinated group should remain elevated regardless of whether the time window between exposure and clinical disease expression is defined as 15 days or 3 years. However, *our findings are consistent with vaccines acting as a proinflammatory cofactor in individuals with subclinical autoimmunity* because this mechanism would be expected to hasten symptom onset but not change the long-term risk of developing MS or [clinically isolated syndrome].

(*Id*. at 7 (emphasis added).) In conclusion, the Langer-Gould authors explained that "[i]n younger patients, we observed a short-term increase in risk after vaccination of any type, which suggests that vaccines (like infections) may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease." (*Id*.)

Consistent with that Langer-Gould observation, Dr. Steel opined that in petitioner's case "[t]he vaccinations likely did not cause the MS but rather unmasked it, i.e. caused it to become clinically significant during her medical evaluation. Clinically

[10] This exhibit was designated as Ex. 63 when filed. (ECF No. 57.) However, this is incorrect, and the exhibit should be Ex. 62 in accord with the updated exhibit list. (ECF No. 57-1.)

asymptomatic MS is termed *radiographically isolated syndrome (RIS).* The term RIS refers to people with no symptoms or abnormalities on neurological examination who have lesions typical for MS on MRI scans. This phenomenon is relatively common. Following the attack of myelitis, [petitioner] meets current diagnostic criteria for Multiple Sclerosis. She experienced a clinically symptomatic event in a limited time window following vaccinations. This event, called a *Clinically Isolated Event,* was her first episode of neurological symptoms typical of an MS relapse in a person not known to have MS." (Ex. 20, p. 3 (emphasis original).)

In addressing the Langer-Gould article, Dr. Sriram offered no critique of the value or methodology of the study but contended that the study's overall finding against causality is contrary to petitioner's claim. (Ex. O, p. 5.) Dr. Sriram suggests that Dr. Steel "misquotes" the Langer-Gould study (*Id.*), but I do not see where this is the case.[11] Dr. Steel's discussion of the paper appears accurate and Dr. Steel has offered no opinion that vaccinations *initially cause* MS in healthy patients. Rather, Dr. Steel agreed in his first report that "there is little evidence that vaccinations cause multiple sclerosis in healthy patients" and in his second report confirmed that he has "made no assertion of a causal relationship between the vaccines and MS." (Ex. 20, p. 5; Ex. 54, p. 1.) As noted above, he opined that the etiology of demyelinating conditions is multifactorial. Although Dr. Sriram considers the cause of autoimmunity in MS to be enigmatic and does not endorse the mechanism proposed by the Langer-Gould authors, that mechanism of vaccine involvement as an inflammatory cofactor is potentially consistent with Dr. Sriram's own description of MS as developing due to T-lymphocyte inflammation of the central nervous system.

Critically, this also remains consistent with petitioner's burden of proof for a significant aggravation claim. Petitioner need only demonstrate that her vaccination

[11] By "misquote" it appears Dr. Sriram may refer to the fact that petitioner was not under 50 years of age and did not experience symptom onset within 30 days of vaccination. (Ex. O, p. 5.) While these points are both correct, they do not call the validity of the study into question. Nor am I persuaded that they are meaningful barriers to petitioner's reliance on this study in this case, especially with regard to *Althen* prong one/*Loving* prong four, which speaks to general medicine only. That a statistically significant risk was found remains evidence that vaccines are a relevant antecedent event. That is, it is evidence tending to show that vaccines did contribute to significantly aggravate subclinical autoimmunity into overt MS among the examined population. Importantly, however, this is only a statistical observation. Nothing in the Langer-Gould paper purports to set an outside limit of 30 days for the expected reaction to occur. Rather, the study only suggests that the rate of onset occurring within 30 days post-vaccination resulted in an identifiable, statistically significant cluster. With regard to petitioner's age, the Langer-Gould authors strongly suggest their finding was age limited primarily due to the limits of their study population. They explained that they separately examined the association among those over and under age 50 precisely because new onset of MS after age 50 is rare overall and further indicated that the study was limited by a small number of older individuals. (Ex. 62, pp. 3, 7.) Nothing in the substance of the article, nor Dr. Sriram's reports, indicates any reason why the mechanism hypothesized would be age dependent. Dr. Sriram has likewise cited literature in this case showing that despite an unexplained increase in incidence of MS among women over 50 years or age over several decades, mean age of initial onset remains 36.2 years of age (up from 32.6 during the 1950's). (Nils Koch-Henriksen et al., *Incidence of MS has Increased Markedly Over Six Decades in Denmark Particularly with Late Onset and in Women*, 90 NEUROLOGY e1954 (2018) (Ex. N, p. 5 (Table 1)).)

affected her condition; she does not have a burden to demonstrate that her ultimate condition is worse than her expected outcome. *Sharpe v. Sec'y of Health & Human Servs*., 964 F.3d 1072, 1081 (Fed. Cir. 2020). Moreover, it is well established that petitioner need only demonstrate that her vaccine was a substantial contributing factor to her injury rather than the sole cause of injury. *Shyface*, 165 F.3d at 1353 (explaining that although the Shyfaces did not prove that the DPT vaccine was the only or predominant cause of his death, the requirements of the Vaccine Act are met *prima facie* upon proof of the substantial factor criterion.). That is, petitioner's vaccination need not explain her entire clinical history of MS in order to have affected her condition in the context of her immediate post-vaccination clinical attack.[12] Nor must the vaccination be the sole cause of her clinical attack. *Accord Quackenbush v. Sec'y of Health & Human Servs*., No. 14-1000V, 2018 WL 1704523 (Fed Cl. Spec. Mstr. Mar. 14, 2018) (finding that petitioner satisfied the *Loving* test to demonstrate that the flu vaccine significantly aggravated petitioner's pre-existing MS).

Although Dr. Sriram has cited literature that includes discussion of epidemiologic evidence generally weighing against the idea of vaccine-related MS, including evidence speaking both to initial onset and to clinical worsening or relapsing of MS,[13] such evidence does have limitations.[14] I am not prepared on this record to conclude that this

[12] I also note that, although she experienced a period of some improvement, the medical records reflect that the sequela of petitioner's first clinical attack of MS likely persisted for more than six months. (*See e.g.*, Ex. 9, pp. 6-7; Ex. 15, p. 21; Ex. 50, p. 4; Ex. 51, p. 57.)

[13] Specifically: Ex. A, pp. 9-10 (citing Mia Topsoe Mailand & Jette Lautrup Frederiksen, *Vaccines and Multiple Sclerosis: A Systemic Review*, 264 J Neurol 1035 (2017) (Ex. E); Giovanni Ristori et al., *Effects of Bacille Calmette-Guerin After the First Demyelinating Event in the CNS,* 82 Neurology 41 (2013) (Ex. F); Ellen Bible, *Multiple Sclerosis: Disease Activity is Reduced in CIS After BCG Vaccination*, 10 NATURE REVIEWS Neurology 62 (2014) (Ex. G); Frank De Stefano et al., *Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults*, 60 ARCH NEUROL 504 (2003) (Ex. H); Mauricio F. Farez & Jorge Correale, *Immunizations and Risk of Multiple Sclerosis: Systemic Review and Meta-Analysis*, 258 J Neurol 1197 (2011) (Ex. I); Alexander Hapfelmeier et al., *A Large Case-Control Study on Vaccination as Risk Factor for Multiple Sclerosis*, 93 NEUROLOGY e916 (2019) (Ex. J); Miguel A. Hernan, Alvaro Alonso & Sonia Hernandez-Diaz, *Tetanus Vaccination and Risk of Multiple Sclerosis*, 67 NEUROLOGY 212 (2006) (Ex. K); Christian Confavreux et al., *Vaccinations and the Risk of Relapse in Multiple Sclerosis*, 344 N. ENGL. J. MED 319 (2001) (Ex. P).)

[14] For example, Farez and Correale, explain that meta-analyses of pooled data have significant limitations and must be interpreted with caution. (Farez & Correale, *supra*, at Ex. I, p. 7.) Moreover, a chart in their paper characterizes the quality of data available from many underlying studies as either unclear, unavailable, or of only low to moderate quality. (*Id*. at 8.) Additionally, a review article filed by petitioner notes that although the Institute of Medicine has rejected a causal relationship between MS and common vaccinations including tetanus, there is separate evidence of vaccines being associated with MS relapses, most notably vaccines against HPV and yellow fever. (Dimitrios Karussis & Panayiota Petrou, *The Spectrum of Post-Vaccination Inflammatory CNS Demyelinating Syndromes*, 13 Autoimmunity Reviews 215 (2014) (Ex. 60, p. 6.) Accordingly, the record of this case demonstrates that the epidemiologic evidence is not in complete agreement, leaving generalizations difficult. A further issue highlighted by this article is the fact that, although there is a "nonnegligible" risk of CNS demyelination following vaccination, that risk is far lower than the risk of CNS demyelination resulting from the infections vaccinations are intended to prevent. (*Id*. at 7.) One cited study observed a 30% risk of developing CNS demyelination after influenza infection versus a 5% risk following influenza vaccination. (*Id*. at 6.) This complicates the statistical observations of studies that purport to find no increased risk of CNS

type of evidence defeats petitioner's presentation of a reasonable expert discussion of the mechanism of vaccine-affected inflammation leading to autoimmune CNS demyelination coupled with a significantly sized case controlled study of unchallenged quality purporting to detect a statistically significant risk of clinical manifestation of MS following vaccination. Dr. Steel likewise agrees that the epidemiological evidence indicates that "MS, a chronic, recurrent and progressive disorder, is not likely caused by any single immune insult event." (Ex. 20, p. 4.) However, Dr. Steel also cautioned that "since all vaccine injuries are quite rare relative to the total number of vaccinations administered . . . [i]t is possible for a given adverse event to occur, but not to occur with sufficient frequency to produce an epidemiological signal."[15] (Ex. 54, p. 7.) He also suggested that "[t]he dissemination of MS clinical events in time means that relating onset of symptoms to specific immune challenges is difficult, and it is likely that triggering of clinically significant MS by vaccine is underreported for this reason." (Ex. 20, p. 4.) Mailand and Fredericksen, a literature review on vaccines and MS that is often cited as authoritative and was relied upon by Dr. Sriram in this case, agrees, noting that:

> Another problem of studying MS risk factors is the lag between onsets of the initial symptoms and final diagnosis. Time between symptoms and diagnosis varies considerably depending on several factors, including individual health-seeking behaviour, health care systems, diagnostic techniques, etc. As a result, studies with short follow-up have a risk of disregarding potential association. However, studies with a too long follow-up risk diluting a potential association or to find false positive association due to subsequent triggers. Finally, manifestations of MS vary significantly between patients, making it difficult to compare the course of the disease.

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demyelination among vaccinated groups compared to controls without accounting for infectious illnesses. For example, DeStefano et al, a study cited by Dr. Sriram, purported not to find any association between several vaccinations and onset of MS. (De Stefano et al., *supra*, at Ex. H, p. 1.) That study controlled for age, sex, HMO status, race, ethnicity, ancestry, family medical history, education, material status, occupation, residence history, cigarette smoking, pet ownership, etc. (*Id*. at 2.) Yet, there is no indication that they screened subjects for their health status relating to illness or infection despite identifying infection as potentially relevant to the pathogenesis of MS. For all these reasons, it is significant that only a fraction of the broader body of epidemiological studies discussed by the review literature has been filed in this case.

[15] Interestingly, Dr. Sriram goes still further, stressing that certain of the prior epidemiologic studies suggest not the lack of any association but instead that tetanus vaccine has a protective effect against MS. (Ex. A, pp. 9-10.) He similarly stresses that "[a]s clinicians we don't withhold immunizations on the belief that [vaccinations] may 'trigger' relapses in MS patients." (Ex. A, p. 15.) This is confounded by the possibility of infection being the more significant risk as compared to vaccination as noted in n. 14, *supra*. That vaccines protect against the still greater risk does not mean that they are themselves entirely risk free. Dr. Sriram has presented this logic in prior cases and it has been rejected. *Jane Doe/74,* 2010 WL 2788239, *infra*. Mailand and Fredericksen, a literature review relied upon by Dr. Sriram, likewise identifies the potential protective effect of tetanus vaccination, but explains that many of the relevant studies lack statistical power or contain confounding factors. (Ex. E, p. 12.) They explain that the protective effect "might exist" but that further study is necessary. (*Id.*)

(Ex. E, p. 14.)

In any event, the Federal Circuit has previously stressed that a petitioner is not obligated to present an epidemiological case supporting her claim. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). As noted above, petitioner's burden is to provide a legally probable rather than medically certain theory of causation. The Langer-Gould findings add to the body of epidemiology even as that body of epidemiology tempers the findings of any one study. In fact, the Langer-Gould authors assert that "[o]ur findings reconcile the anecdotal clinical reports of a CNS ADS onset shortly after vaccination with the larger body of epidemiologic literature showing no long-term increase of MS or other forms of CNS ADS following vaccination." (Ex. 62, p. 7.) Notable in that regard, Mailand and Frederiksen does include the Langer-Gould study among its review of the relevant body of literature. However, Mailand and Frederiksen, like Dr. Sriram, only address the long-term findings of Langer-Gould as weighing against a causal relationship and do not address at all the specific short-term finding highlighted by Dr. Steel and discussed in this decision. Again, this underscores the difficulty posed by seeking to rely on review literature given the record of this case. It also raises the question of what additional findings may be contained in the studies reviewed by Mailand and Frederisksen (and other literature reviews) that were not explicitly discussed.

With regard to specific studies that were filed in this case, respondent also suggests that the study by Destefano et al, should be preferred to Langer-Gould in terms of the specific findings regarding a short-term association between vaccinations and clinical manifestation of MS. (ECF No. 70, n. 12.) However, respondent has not articulated any basis for preferring one study over the other in terms of the quality or validity of the studies themselves. Notably, the Langer-Gould study was conducted more recently than the Destefano study. The Langer-Gould authors reviewed and discussed the prior Destafano study and explained that it was limited by the small number of vaccinated cases, incomplete case-finding methods, imprecise estimates or unclear timing of onset, confounding factors such as healthcare utilization, and undefined delay between vaccination and symptom onset. (Ex. 62, p. 2.) Although the Langer-Gould study likewise has limitations, the study authors suggest that "[o]ur study overcomes many of the methodological limitations of previous MS vaccine safety studies with a larger sample size, rigorous case-finding methods, inclusion of MS precursors, prospectively recorded symptom onset dates, and complete vaccination records." (*Id*. at 7.) Respondent also cited Confavreux et al., as being consistent with Destefano, et al. (ECF No. 70, n. 12.) The Langer-Gould authors did not address the earlier Confavreux study. The Confavreux study is closer in size to Langer-Gould; however, the case-crossover model of the Confravreux study, in which different periods are examined such that the subjects act as their own controls, would seem to make direct comparisons to Langer-Gould difficult.

Notably, the Federal Circuit's *Althen* decision itself affirmed the decision in *Althen* which involved a tetanus toxoid vaccine causing CNS demyelinating disease in the form

of ADEM and optic neuritis.[16] *See generally Althen*, 418 F.3d 1274. Since then, there have been several cases where special masters ruled in favor of petitioners who developed demyelinating disease after vaccination, including cases linking both TM and MS to tetanus vaccines. *See Smith v. Sec'y of Health & Human Servs.*, No. 08–864V, 2016 WL 2772194 (Fed. Cl. Spec. Mstr. Apr. 18, 2016) (awarding compensation for MS linked to a hepatitis B vaccine); *Jane Doe/74 v. Sec'y of Health & Human Servs.*, No. [Redacted], 2010 WL 2788239 (Fed. Cl. Spec. Mstr. June 28, 2010) (awarding compensation for TM and MS linked to tetanus-diphtheria and measles-mumps-rubella ("MMR"), hepatitis B, and meningococcal vaccines); *Johnson v. Sec'y of Health & Human Servs.*, No. 99–219V, 2000 WL 1141582 (Fed. Cl. Spec. Mstr. Jul. 27, 2000) (awarding compensation for ADEM linked to a tetanus-diphtheria ("Td") vaccine); *Hargrove v. Sec'y of Health & Human Servs.*, No. 05–694V, 2009 WL 1220986 (Fed. Cl. Spec. Mstr. Apr. 14, 2009 (awarding compensation for TM linked to a diphtheria-tetanus-acellular pertussis ("DTaP") vaccine and/or other vaccinations); *Werderitsh v. Sec'y of Health & Human Servs*., No. 99–310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006) (awarding compensation for MS linked to a hepatitis B vaccine).

ii. Logical sequence of cause and effect showing the vaccination was the reason for the injury (*Althen* prong two/*Loving* prong five)

The second *Althen* prong/fifth *Loving* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). However, medical records and/or statements of a treating physician do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* 42 U.S.C. §300aa-13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

In light of all of the above analysis, this aspect of petitioner's claim does not need be addressed at length. Consistent with all of the above, both petitioner's and respondent's respective experts agree that prior to vaccination petitioner's MS was clinically silent and that after vaccination she suffered a clinical attack of her MS

[16] Although CNS demyelinating conditions are not entirely interchangeable, in some instances the precise diagnosis has not been dispositive of the causation analysis. *E.g.*, *Samuels*, 2020 WL 2954953 at *19 (noting that "this is not a case where defining the injury is key to its resolution."); *Harmon v. Sec'y of Health & Human Servs*., No. 12-298V, 2017 WL 2872293, at *22 (Fed. Cl. Spec. Mstr. June 6, 2017) (finding that petitioner suffered "a CNS demyelinating condition, most likely an atypical form of multiple sclerosis."); *Hitt v. Sec'y of Health & Human Servs*., No. 15-1283V, 2020 WL 831822, at n.8 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) (finding preponderant evidence of an initial diagnosis of transverse myelitis followed by a subsequent diagnosis of multiple sclerosis, but noting that "the importance of the diagnosis is diminished" by respondent's expert's agreement that either condition can be caused by the flu vaccine.).

consistent with an acute presentation following an antecedent event. (Ex. 20, pp. 3, 5; Ex. 54, pp. 1, 6-7; Ex. A, pp. 7-8, 13.) Specifically, Dr. Steel opined that prior to vaccination petitioner's condition was best characterized as radiographically isolated syndrome, but that she "experienced a clinically symptomatic event in a limited time window following vaccinations." He indicated that following this post-vaccination myelitis, petitioner met the diagnostic criteria for MS based on this clinically isolated event. (Ex. 20, p. 3.) Although Dr. Sriram did not agree petitioner's vaccinations were a relevant event, he similarly opined more generally that petitioner's "enhancing lesions suggested a recent acute event." (Ex. O, p. 7.) Treating physician opinions in this case are less helpful due to the uncertainty surrounding their diagnoses. Those who discussed causal factors tended to view petitioner's condition as ADEM.

iii. Proximate temporal relationship between vaccination and injury (*Althen* prong three/*Loving* prong six)

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11–355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

As explained above, petitioner experienced an attack of CNS demyelination less than two months following the vaccinations at issue in this case. (Ex. 2, p. 51, 59; Ex. 8, p. 2.) More specifically, on June 5, 2016, petitioner sought treatment at Capital Health Regional Medical Center emergency room for right side weakness and numbness, which began two nights prior, i.e. June 3, 2016.[17] (Ex. 2, p. 51, 59.) June 3, 2016 was approximately 60 days following her April 4, 2016 polio vaccination and 42 days following her April 22, 2016 Tdap vaccination. (Ex. 1.)

Petitioner has filed literature which indicates that, while CNS demyelination often occurs within three to four weeks of vaccination, it has previously been shown to occur up to six months following vaccination. (Karussis & Petrou, *supra*, at Ex. 60, p. 7.) This provides some evidence supporting a temporal relationship. *E.g.*, *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) ) (stating that "[t]he special master further erred in setting a hard and fast deadline" for onset and noting that

[17] The previously assigned special master characterized onset as occurring June 4, 2016, but did not specify the basis for that conclusion. (ECF No. 9, p. 2.)

the medical literature filed in the case "do not purport to establish any definitive timeframe for onset of clinical symptoms."). But perhaps more significantly, onset in this case is also consistent with prior cases that have identified the relevant temporal period for vaccine-related CNS demyelination, including MS and ADEM, as being up to about 42 days, comparing that period to the timing of adaptive immune response otherwise commonly accepted for peripheral demyelinating conditions such as Guillain-Barre Syndrome ("GBS"). *See e.g.*, *Smith*, 2016 WL 2772194, at *18; *Quackenbush*, 2018 WL 1704523, at *20. Other cases involving GBS have in turn found a period of up to about two months to be medically reasonable for autoimmune demyelination. *Barone v. Sec'y of Health & Human Servs.*, No. 11-707V, 2014 WL 6834557, at *13 (Fed. Cl. Spec. Mstr. Nov. 12, 2014).

Importantly, although the above-discussed Langer-Gould study found that the association between vaccination and clinical onset of MS that they observed disappeared after 30 days, this is only a statistical observation relating to risk. (Langer-Gould et al., *supra*, at Ex. 62, pp. 5, 7.) The ability to identify a 30-day window in which a disproportionate number of cases see onset of clinical symptoms provides evidence that the vaccination is a relevant and identifiable antecedent event. It does not, however, purport to identify any outside limit for the pathologic process at work. Rather, the period routinely recognized in his program as medically reasonable for the manifestation of autoimmune demyelination, and especially CNS demyelination, remains the controlling consideration with regard to *Althen* prong three. The experts agree that it is the fact that inflammation results in demyelination that leads to outward disability.

## VI. Conclusion

For all the reasons discussed above, after weighing the evidence of record within the context of this program, there is preponderant evidence that petitioner's multiple sclerosis was significantly aggravated as a result of her receipt of the tetanus, diphtheria, and pertussis ("Tdap") vaccination administered on April 22, 2016 and/or the polio vaccination administered on April 4, 2016. A separate damages order will be issued.

**IT IS SO ORDERED.**

**s/Daniel T. Horner**
Daniel T. Horner
Special Master