In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 30, 2023

MINH LE,	*	PUBLISHED
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Petitioner,	*	No. 16-1078V
	*	
v.	*	Special Master Nora Beth Dorsey
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus-Diphtheria-Acellular Pertussis ("Tdap") Vaccine; Transverse Myelitis ("TM").
	*	
Respondent.	*	
	*	

Maximillian J. Muller, Muller Brazil, LLP, Dresher, PA, for Petitioner.
Alec Saxe, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

I. INTRODUCTION

On August 29, 2016, Minh Le ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2012).[2] Petitioner alleges that he developed transverse myelitis ("TM") as the result of a tetanus-diphtheria-acellular pertussis ("Tdap") vaccination administered on May 20, 2014. Petition at 1 (ECF No. 1). Respondent argued against compensation, stating that "this

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

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

case is not appropriate for compensation under the terms of the Vaccine Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 36).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has provided preponderant evidence that his Tdap vaccine caused his TM, satisfying Petitioner's burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, Petitioner is entitled to compensation.

II. ISSUES TO BE DECIDED

Diagnosis is not at issue. See Resp. Pre-Hearing Brief, filed Feb. 25, 2022, at 2 (ECF No. 105) (acknowledging that "[P]etitioner has been diagnosed with [TM]"). The central issue is causation: "(1) whether the Tdap vaccine can cause [TM]; (2) whether [P]etitioner's [TM] was caused by receipt of the vaccination at issue, and; (3) whether the time between [P]etitioner's vaccinations and the onset of symptoms would be considered 'medically acceptable to infer causation-in-fact.'" Joint Pre-Hearing Submission, filed Feb. 2, 2022, at 2 (ECF No. 98). Petitioner contends he has provided preponderant evidence that his Tdap vaccine caused his TM, satisfying all three Althen prongs. Petitioner's ("Pet.") Pre-Hearing Brief, filed Jan. 18. 2022, at 8-17 (ECF No. 97). Respondent disagrees and argues that Petitioner failed to provide "sufficiently reliable evidence of causation that satisfies the elements of Althen." Resp. Pre-Hearing Brief at 11-25.

III. BACKGROUND

A. Medical Terminology

TM is "a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord, resulting in varying degrees of weakness, sensory alterations[,] and autonomic dysfunction." Pet. Exhibit ("Ex.") 8.8 at 1;[3] Pet. Ex. 11.6 at 1;[4] see also Pet. Ex. 11.9 at 1.[5] TM may be an acute process, or a "slow subacute process." Pet. Ex. 11.1 at 2.[6] In the acute presentation, symptoms usually "develop over several hours and then worsen over one to several days." Id. "Bilateral weakness and sensory symptoms below the level of the [TM] lesion

[3] N. Agmon-Levin et al., Transverse Myelitis and Vaccines: A Multi-Analysis, 18 Lupus 1198 (2009). This is also cited by Respondent as Resp. Ex. C, Tab 4.

[4] Chitra Krishnan et al., Transverse Myelitis: Pathogenies, Diagnosis and Treatment, 9 Frontiers Bioscience 1483 (2004). This is also cited by Respondent as Resp. Ex. C, Tab 1.

[5] Bruce A.C. Cree & Dean M. Wingerchuk, Acute Transverse Myelitis: Is the "Idiopathic" Form Vanishing?, 65 Neurology 1857 (2005).

[6] Anupama Bhat et al., The Epidemiology of Transverse Myelitis, 9 Autoimmunity Revs. A395 (2010).

are typical. . . . Bowel and bladder dysfunction, reflective of autonomic involvement, [can] also occur." Id.

Many of the references filed by the parties describing TM characterize the presentation at onset similarly. See, e.g., Pet. Ex. 11.8 at 1 (describing acute TM as being characterized by "symptoms and signs of neurologic dysfunction resulting in weakness, sensory loss[,] [] and autonomic dysfunction");[7] Pet. Ex. 8.7 at 2 (noting TM is "characterized by acute or sub acute motor; sensory; and autonomic (bladder; bowel; and sexual) spinal cord dysfunction");[8] Resp. Ex. A, Tab 2 at 1 (explaining that inflammatory myelopathies can present as "bilateral weakness and sensory changes below the spinal cord level of injury, often accompanied by bowel and bladder impairment");[9] Pet. Ex. 11.3 at 1 (describing a study where "[p]atients were considered as having severe initial symptoms [of acute TM] if they were unable to walk or had urinary incontinence or required catheterization").[10]

This is consistent with the inclusion criteria developed by the TM Consortium Working Group which identifies "[d]evelopment of sensory, motor, or autonomic dysfunction attributable to the spinal cord" as criteria for diagnosis. Pet. Ex. 11.5 at 2 tbl.1.[11] Sensory dysfunction is described as "numbness, paresthesias,[12] or band-like dysesthesias."[13] Id.

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[7] Sean J. Pittock & Claudia F. Lucchinetti, Inflammatory Transverse Myelitis: Evolving Concepts, 19 Neurology 362 (2006).

[8] Avinash Chandra et al., Vaccine Induced Acute Transverse Myelitis: Case Report, 6 J. Neurology & Stroke 197 (2017).

[9] Bruce A.C. Cree, Acute Inflammatory Myelopathies, in 122 Handbook Clinical Neurology 613 (D.S. Goodin ed., 2014).

[10] J. de Seze et al., Idiopathic Acute Transverse Myelitis: Application of the Recent Diagnostic Criteria, 65 Neurology 1950 (2005).

[11] Transverse Myelitis Consortium Working Grp., Proposed Diagnostic Criteria and Nosology of Acute Transverse Myelitis, 59 Neurology 499 (2002). This is also cited by Respondent as Resp. Ex. A, Tab 1.

[12] Paresthesia is "an abnormal touch sensation, such as burning, prickling, or formication, often in the absence of an external stimulus." Paresthesia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=37052 (last visited Mar. 22, 2023).

[13] Dysesthesia is the "distortion of any sense, especially of that of touch" or "an unpleasant abnormal sensation produced by normal stimuli." Dysesthesia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=15186 (last visited Mar. 22, 2023).

TM can be accompanied by magnetic resonance imaging ("MRI") signaling abnormality in the spinal cord, cerebrospinal fluid ("CSF") pleocytosis,[14] and/or oligoclonal bands[15] in the CSF. Pet. Ex. 11.5 at 1.

"The pathogenesis of TM is probably of an autoimmune nature, whether TM presents as an isolated disorder or as part of a systemic disease." Pet. Ex. 8.8 at 1. TM has been associated with viral infections, autoimmune disorders, and vaccinations. Id. at 2-3; Pet. Ex. 11.1 at 2-4; Resp. Ex. A, Tab 9 at 3.[16]

B. Procedural History

Petitioner filed his petition, supporting medical records, and a letter from treating physician, Dr. Wesley Chay, on August 29, 2016. Petition; Pet. Exs. 1-6. Petitioner filed additional medical records and an expert report by Dr. John Conomy on May 3, 2017. Pet. Exs. 7-8. On August 2, 2017, Petitioner filed his affidavit. Pet. Ex. 10. Petitioner filed an expert report by Dr. M. Eric Gershwin on August 7, 2017. Pet. Ex. 11. Additional medical records were filed in August and September 2017.[17] Pet. Exs. 10-16. Respondent filed his Rule 4(c) Report, arguing against compensation, on July 20, 2018. Resp. Rept. at 2. That same day, Respondent filed an expert report by Dr. Jeffrey Gelfand. Resp. Ex. A.

On September 21, 2018, Respondent filed an expert report from Dr. Thomas Forsthuber. Resp. Ex. C. Petitioner filed a supplemental report from Dr. Gershwin on January 11, 2019. Pet. Ex. 18. On June 10, 2019, Petitioner filed an expert report from Dr. Maria Chen. Pet. Ex. 19. And on November 13, 2019, Petitioner filed a second supplemental report from Dr. Gershwin. Pet. Ex. 21. On March 27, 2020, Respondent filed a supplemental expert report from Dr. Forsthuber. Resp. Ex. E. Subsequently, on August 3, 2020, Petitioner filed a supplemental expert report from Dr. Chen and a third supplemental expert report from Dr. Gershwin. Pet. Exs. 22-23.

The case was reassigned to the undersigned on July 30, 2020. Notice of Reassignment, filed Aug. 3, 2020 (ECF No. 61). A Rule 5 status conference was held on October 20, 2020.

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[14] Pleocytosis is the "presence of a greater than normal number of cells in the cerebrospinal fluid." Pleocytosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=39556 (last visited Feb. 8, 2023).

[15] Oligoclonal bands are "discrete bands of immunoglobulins with decreased electrophoretic mobility; their appearance in … cerebrospinal fluid when absent in the serum is a sign of possible multiple sclerosis or other diseases of the central nervous system." Oligoclonal Bands, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=60106 (last visited Feb. 8, 2023).

[16] Roger Baxter et al., Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis, 63 Clinical Infectious Diseases 1456 (2016).

[17] Additional medical records were filed throughout the course of litigation.

Rule 5 Order dated Oct. 20, 2020 (ECF No. 65). The undersigned agreed with the parties that TM was the correct diagnosis. Id. at 1. The undersigned found Petitioner's experts had competing theories for a mechanism of causation but preliminarily found molecular mimicry to be sound. Id. at 2. Additionally, the undersigned preliminarily found onset to be approximately three days and that it was appropriate given Petitioner's theory. Id. The undersigned ordered that the parties consider settlement negotiations, and by February 2021, the case was referred to the alternative dispute resolution ("ADR") program. Id.; Order dated Feb. 16, 2021 (ECF No. 73). However, by April 2021, the case was removed from ADR because it could not be resolved informally "in light of the parties' positions." Order dated Apr. 1, 202 (ECF No. 76).

At a status conference on May 20, 2021, the parties agreed to resolve this matter through an entitlement hearing. Order dated May, 20, 2021 (ECF No. 78); see also Order dated June 21, 2021 (ECF No 82). On July 16, 2021, Petitioner filed a final expert report by Dr. Lawrence Steinman, and on November 8, 2021, Respondent filed a supplemental expert report by Dr. Gelfand. Pet. Ex. 25; Resp. Ex. F.

Petitioner filed his pre-hearing brief on January 18, 2022, and Respondent filed his pre-hearing brief on February 25, 2022. Pet. Pre-Hearing Brief; Resp. Pre-Hearing Brief. An entitlement hearing was held on March 15 and 16, 2022 via Zoom videoconference. See Transcript ("Tr."). Petitioner and Drs. Steinman, Gershwin, Gelfand, and Forsthuber testified. Tr. 3, 216. Thereafter, additional medical literature was filed by both parties. Pet. Exs. 11.78, 50-51; Resp. Exs. J-L. Petitioner subsequently filed a post-hearing brief. Pet. Post-Hearing Brief, filed July 15, 2022 (ECF No. 123). Thereafter, Respondent filed a post-hearing brief and Petitioner filed a reply. Resp. Post-Hearing Brief, filed Sept. 13, 2022 (ECF No. 126); Pet. Reply to Resp. Post-Hearing Brief ("Pet. Reply"), filed Oct. 13, 2022 (ECF No. 127).

This matter is now ripe for adjudication.

C. Factual History

1. Medical History

On Tuesday, May 20, 2014, at 46 years of age, Petitioner received a Tdap vaccine in his right deltoid at or around 5:51 PM. Pet. Ex. 1 at 5, 8, 10. Petitioner had presented to the emergency department ("ED") for a finger laceration on his left hand caused by a metal object. Id. at 4, 9-10. There were no other complaints, and on examination, there were no signs of focal neurologic deficits or other conditions. Id. at 10-11. In addition to the Tdap vaccine, Petitioner received sutures and was prescribed Keflex.[18] Id. at 4, 11-12.

[18] Keflex is "trademark for preparations of cephalexin." Keflex, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=26786 (last visited Mar. 23, 2023). Cephalexin is an antibiotic "effective against a wide range of gram-positive and a limited range of gram-negative bacteria; administered orally in the treatment of . . . infections of the genitourinary tract, of bones and joints, and of skin and soft tissues." Cephalexin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=8629 (last visited Mar. 23, 2023).

Four days later, on Saturday, May 24, 2014, Petitioner presented to the ED for the inability to walk or feel while urinating. Pet. Ex. 2 at 20. The first history taken appears to be a Triage note documented at 9:21 AM, which stated that Petitioner began taking an antibiotic "on Tuesday night and started getting stiffness and pain in lower extremities." Id. His symptoms progressively worsened, and he was "now unable to walk or urinate." Id. A subsequent history taken by Tiesha McGee, registered nurse ("RN"), at 9:33 AM, noted "[Petitioner] state[d] that he started new meds on Tues[day], [Petitioner] state[d] that he began having lower back pain and difficulty walking yesterday." Id. at 28. Nurse McGee observed that Petitioner's gait was unsteady but he was "able to weight bear." Id. at 29.

Attending ED physician, Dr. Ajay Singhal, along with physician assistant, Christine Kerrigan, saw Petitioner by 3:01 PM. Pet. Ex. 2 at 29. Ms. Kerrigan documented that Petitioner reported "[bilateral] [lower extremity] weakness and urinary retention worsening [for] 3 d[ays], unable to stand or void since 3:00 AM this morning." Id. at 21, 28 (noting "[a]scending weakness [in] both legs over last 3 days"). Petitioner described his symptoms as "generalized weakness" that had been getting progressively worse, and as of 3:00 AM that morning (May 24), he was unable to stand/walk or urinate, stating "nothing comes out." Id. at 20-21. He also complained of associated midback pain. Id. at 21, 28. On physical examination, Petitioner was "unable to bear weight when standing" and had "decreased sensation up to just above left knee[,] though [right] leg sensations seem[ed] ok." Id. at 22, 28.

After the ED physician consulted with neurologist Dr. Joshua Khoury, Petitioner underwent a lumbar puncture and MRI of the thoracic and lumbar spine that same day, May 24.[19] Pet. Ex. 2 at 25, 28. The thoracic spine MRI revealed "a long segment of abnormal central cord signal extension from T2 down to T9, with slight expansion of the cord at C6-7." Id. at 4, 78-79. There was "minimal enhancement of the cord at T6." Id. The CSF analysis from the lumbar puncture revealed slightly elevated protein level of 56 and two oligoclonal bands[20] that were not present in the serum. Id. at 6, 14, 28, 42-43. The CSF was negative for Lyme disease, cytomegalovirus ("CMV"), and other diseases, and the culture did not show any growth, indicating there were no abnormalities or results consistent with infection. Id. at 43-45. Petitioner was diagnosed with TM and admitted for further treatment. Id. at 25, 28.

The next day, on May 25, 2014, Petitioner was evaluated by neurologist Dr. Khoury. Pet. Ex. 2 at 3-4. Dr. Khoury's history stated that "[t]his past Wednesday, approximately 4 days ago [Petitioner] began to develop symptoms that he describe[d] as stiffness in the bilateral lower extremities part. It started distally and moved proximally over a period of several days. He describe[d] a weakness as well as heaviness in bilateral legs." Id. at 3. Additionally, Petitioner

[19] A computerized tomography ("CT") scan of Petitioner's brain was also performed but was unremarkable. Pet. Ex. 2 at 27.

[20] The Oligoclonal Band Report stated, "The patient's CSF contains 2 well defined gamma restriction bands that are not present in the patient's corresponding serum sample. These bands indicated abnormal synthesis of gammaglobulins in the central nervous system." Pet. Ex. 2 at 43.

reported that "[a]pproximately 2 to 3 days ago, he began to notice that he was unable to void his urine." Id. Dr. Khoury noted the finger laceration and Tdap shot Petitioner received "approximately 5 to 6 days ago." Id. On physical examination, Petitioner demonstrated a "reduced vibratory sense in the bilateral extremities" and a "very soft sensory level at approximately the T10 area." Id. Petitioner denied any upper extremity symptoms. Id. Dr. Khoury's impression was that Petitioner's MRI was "consistent with an underlying [TM]." Id. at 4. "Whether or not this has to [do] with his recent left-hand laceration, plus-minus, the injection that he got as to whether or not this was a [Tdap] shot [was] unclear" at the time. Id. Because Petitioner reported he felt "approximately 20% better compared with yesterday" after starting with a single dose of intravenous ("IV") Solu-Medrol, Dr. Khoury recommended continuing that, 1g daily, for five days, followed by a prednisone taper. Id.

Petitioner was also seen by an infectious disease specialist, Dr. Richard Tepper, on May 25, 2014. Pet. Ex. 2 at 5-7. The consultation note by Dr. Tepper indicated that "[f]our days ago, late in the day, [Petitioner] felt that his feet were stiff. The feeling progressed proximally. He felt numb. He had difficulty controlling his legs." Id. at 5. And then "[t]wo days ago, [Petitioner] developed pressure in his back. He had difficulty moving his legs and . . . was unable to walk. He was unable to urinate though he felt pressure." Id. Dr. Tepper agreed with Dr. Khoury that the MRI results were consistent with TM. Id. at 6. "[Petitioner] has a large spinal cord lesion, etiology is unclear. It is not clear if this is infectious. [Petitioner] has had no fever, chills, no rashes." Id. Dr. Tepper noted where Petitioner lived, that there are occasionally deer on the property, and that Petitioner mowed his lawn frequently. Id. at 5. Given this, Dr. Tepper stated "[Petitioner] may have been exposed to Lyme disease" but that "[t]his would certainly be an unusual presentation for Lyme disease." Id. at 6. He also noted "[n]othing to suggest herpes zoster. Herpes simplex [virus ("HSV")] to be ruled out." Id. He advised to "continue with steroids," but "would not give antibiotics at this time." Id. Additional laboratory tests were ordered (including checks for Lyme antibody and HSV) and the results "did not show any evidence of infection." Id. at 6, 17.

Dr. Thomas Gillon conducted a follow-up care visit for Petitioner's finger laceration on May 27, 2014. Pet. Ex. 2 at 8-10. Petitioner reported "his finger [felt] slightly stiff, but [there was] no significant pain in his finger." Id. at 8. He indicated he "was doing well until 5 days ago. He started feeling stiffness in his feet and then had progressive migration towards his pelvis and developed urinary retention." Id. Dr. Gillon noted there was a "potential area of skin necrosis," but "no signs of infection other than elevated white count yesterday of 24, which was elevated from 10 the day before." Id. at 8-9. On physical examination, Petitioner was able to lift both legs off the bed. Id. at 9. Petitioner stated he felt "significantly stronger in his lower extremities since admission." Id. Dr. Gillon "[did] not believe that the laceration itself would have played any effect in what sounds like [TM]. . . . However, potential reaction to the [Tdap] shot could be a potential cause of his [TM]." Id. Petitioner appeared to be getting significantly better on steroids without antibiotics. Id.

Also on May 27, 2014, Petitioner had a consultation with urologist, Dr. John Rodgers. Pet. Ex. 2 at 11-12. Petitioner relayed that "[o]ver the last week, he had increasing weakness in his lower extremities to the point that he was unable to walk" and also "unable to urinate." Id. at

11. A foley catheter had been in place since admission. Id. at 5, 11, 17. Dr. Rogers' assessment was "[u]rinary retention due to neurologic situation consistent with [TM]." Id. at 11.

Petitioner was discharged from the hospital on May 30, 2014. Pet. Ex. 2 at 17. Discharge notes included that Petitioner had an MRI of the lumbar spine and brain,[21] that he was evaluated by neurology and infectious diseases specialists, and that a lumbar puncture was done "but did not show any evidence of infection." Id. On being "admitted to the hospital with [TM], an antibiotic, IV fluid, and steroids [were] instituted." Id. Petitioner's condition had "slowly improved." Id. He "became more mobile" and had started physical therapy prior to discharge. Id.

From May 30, 2014 to June 14, 2014, Petitioner received acute inpatient rehabilitation treatment at Moss Rehabilitation Hospital ("Moss Rehabilitation"). Pet. Ex. 3 at 97-99; Pet. Ex. 6 at 7-9. His rehabilitation physician was Dr. Wesley Chay. Pet. Ex. 3 at 99; see also Pet. Ex. 5. Following the five-day course of IV Solu-Medrol, Petitioner transitioned to the oral prednisone taper, as recommended by Dr. Khoury. Pet. Ex. 3 at 97. He remained on this throughout his inpatient rehabilitation. Id. Petitioner was also taking gabapentin at this time for bilateral leg stiffness and was instructed to continue to do so upon discharge. Id. at 98. By the date of discharge, Petitioner was stable and exhibited "moderate independence" with activities of daily living ("ADL") and mobility. Id. He was instructed to continue with physical and occupational therapy in an outpatient setting[22] and to follow up with his primary care physician ("PCP"), Dr. Adam Pasternack, and Dr. Chay. Id. at 99. Petitioner was also instructed to follow up with neurology and urology. Id. at 97-98.

On June 21, 2014, Petitioner presented to Dr. Pasternack and reported he was "80% improved." Pet. Ex. 4 at 3. Dr. Pasternack's diagnosis was acute myelitis. Id. at 4. He instructed Petitioner to follow up and to continue rehabilitation. Id.

On July 24, 2014, Petitioner followed up with Dr. Chay. Pet. Ex. 3 at 92; Pet. Ex. 5 at 55. The initial outpatient evaluation documented "[TM] on [May 24, 2014]" as past medical history. Pet. Ex. 3 at 92. Since discharge from Moss Rehabilitation, Petitioner reported he was "doing well" and indicated he would "likely be finishing up on his outpatient [physical and occupational] therapy next week." Id. Petitioner reported he was managing "self-care and ADLs independently" but that he was still "limited by fatigue/poor endurance." Id. Petitioner reported "some stiffness sensation primarily in the left lower extremity" and that it also felt "swollen." Id. He reported he "used to have stiffness in both legs, but the right leg is almost entirely back to normal, and the left is 30% better than it was." Id. Regarding his bladder, Petitioner had "been performing intermittent catheterization around an hour after voiding, . . . usually 3-4 times a day." Id. On examination, Dr. Chay noted "improvement in sensory level to T7 (light touch)." Id.

[21] Petitioner had an unremarkable brain MRI on May 29, 2014. Pet. Ex. 2 at 74.

[22] On June 16, 2014, Petitioner began outpatient therapy two to three times per week at Moss Rehabilitation. Pet. Ex. 3 at 60-63; Tr. 22.

Petitioner returned to Dr. Chay on August 20, 2014. Pet. Ex. 5 at 53. Dr. Chay cleared him to return to work on light duty restrictions. Id. at 54. And on November 19, 2014, Petitioner was cleared to resume full work duties. Id. at 52. At this visit, Petitioner reported that his "pain/tightness" had improved since the last visit, he had been working on increasing his endurance, and he was now "catheterizing himself once nightly." Id. at 51, 53.

On June 8, 2015, Petitioner had a follow-up outpatient evaluation with Dr. Chay. Pet. Ex. 5 at 45-46. Petitioner reported he had continued getting better and noticed improvement when increasing the dosage of gabapentin. Id. at 45. He no longer required catheterization. Id. Petitioner also reported "intermittent difficulty with achieving and maintaining an erection," and the "sensitivity ha[d] been decreased since the [TM]." Id. He was prescribed Viagra. Id. at 46.

Petitioner continued to return to Moss Rehabilitation for follow-up visits from 2015 to 2019 for continued "neurogenic sensations." Pet. Ex. 17 at 6-10, 17-21; see also Pet. Exs. 13, 20. At a visit on December 1, 2016, it was noted that Petitioner's "[s]ympoms [were] attributed to nontraumatic spinal cord injury, which occurred on [May 24, 2014] as a result of [TM]." Pet. Ex. 17 at 6. Records from Petitioner's PCP in 2020 and 2021 indicated Petitioner continued to take gabapentin daily. Pet. Ex. 24 at 44, 48.

No additional relevant medical records were provided.

2. Petitioner's Affidavit and Testimony

Petitioner recalled he received the Tdap vaccine on May 20, 2014, between 5:00 and 6:00 PM. Pet. Ex. 10 at ¶ 3. Prior to and "[a]t the time of vaccination, [he] was a normal, healthy adult with no neurological medical history." Id. at ¶ 4; see also Tr. 8, 43.

On the night of May 21, Petitioner "noticed some minor stiffness in [his] feet before [he] went to bed" at around 11:00 PM. Pet. Ex. 10 at ¶ 5. That was the only symptom he had that day. Tr. 11. The following day, on May 22, he "experienced some numbness and stiffness in [his] feet and legs" but still went to work and worked a full day. Pet. Ex. 10 at ¶ 5; see Tr. 11, 38. By Friday, May 23, Petitioner's "symptoms became worse. The numbness and weakness had got[ten] worse throughout [his] lower extremities" and he had to leave work early that day. Pet. Ex. 10 at ¶ 6; see Tr. 12, 39. That night, he was "unable to urinate before going to bed." Pet. Ex. 10 at ¶ 6. The next day, May 24, his "symptoms got much worse." Id. at ¶ 7. He woke up and for the first time, was "unable to stand up, walk by [him]self, . . . [un]able to urinate, and [his] foot [was] more stiff." Tr. 13. The night of May 24, Petitioner went to the ED "because of spreading numbness and weakness in [his] lower extremities and the inability to urinate." Pet. Ex. 10 at ¶ 7. When he got to the ED, he told them he "got . . . the tetanus shot, and day by day, [he] lost [] feeling." Tr. 17.

After admission to the hospital, Petitioner underwent various tests was diagnosed with TM. Pet. Ex. 10 at ¶ 8. He continued to complain of "stiffness" from his stomach down to his feet as well as "numbness" sensations. Tr. 23, 25, 32, 35, 40-41. As of the date of his testimony, Petitioner continued to suffer lower extremity weakness, urination issues, and continued to take gabapentin. Tr. 24, 34-35; see also Pet. Ex. 10 at ¶¶ 12-13.

3. Letter from Dr. Wesley Chay

Petitioner filed a letter authored by Dr. Chay dated January 18, 2016. See Pet. Ex. 5. In his letter, Dr. Chay stated that Petitioner had been under his care since his acute inpatient hospitalization at Moss Rehabilitation on May 30, 2014. Id. at 1. Dr. Chay summarized Petitioner's history as presenting to the ED where he received sutures and a Tdap shot for a laceration. Id. Petitioner was then discharged home and "after two days, he started developing tightness and weakness in his legs. This progressed and over the next couple days he also developed [the] inability to urinate." Id. Thereafter, he underwent MRIs and a lumbar puncture which were "consistent with [TM]." Id. Petitioner was treated with IV Solu-Medrol for five days, transitioned to a prednisone taper, and after stabilizing, was discharged to Moss Rehabilitation. Id. Dr. Chay reported that Petitioner made "significant progress during his time" there where he received three hours of occupational and physical therapies daily. Dr. Chay also saw Petitioner in follow-up visits while receiving outpatient treatment. Id.

Dr. Chay is a "board-certified Spinal Cord Injury Medicine physiatrist" and the Clinical Director of the Inpatient Spinal Cord Injury Program at MossRehab. Pet. Ex. 5 at 2. In this capacity, he "see[s] many individuals with spinal cord injury and disease. [He] ha[s] treated many patients with [TM], and in many cases, a direct link to a prodrome infection or recent vaccination is present." Id. He noted the existence of "several cases reported in the medical literature where individuals who received a [Tdap] shot have subsequently developed [TM]." Id. Dr. Chay opined, to a reasonable degree of medical and scientific certainty, that "the [Tdap] shot that [Petitioner] received for a work-related injury was the etiology of [TM] in his case." Id.

D. Expert Reports

1. Petitioner's Expert, Dr. John Conomy[23]

a. Background and Qualifications

Dr. Conomy was a board-certified neurologist. Pet. Ex. 9 at 1. Dr. Conomy received his M.D. from St. Louis University and J.D. from Case Western Reserve University. Id. At the time of writing his expert report, Dr. Conomy was a Clinical Professor of Neurology at the Case Western Reserve University School of Medicine and a clinician at the University Hospitals of Cleveland. Id. at 1-2. He authored countless publications on neurological conditions and related topics. Id. at 36-52.

b. Opinion

Dr. Conomy opined, more likely than not, Petitioner's May 20, 2014 Tdap vaccine caused him to develop TM via molecular mimicry. Pet. Ex. 8 at 2-5.

[23] Dr. Conomy submitted one expert report in this matter. Pet. Ex. 8. He did not testify at the hearing. Dr. Conomy has since passed away.

i. Althen Prong One

Dr. Conomy posited the mechanism of damage to the spinal cord and nervous system in instances of TM by the Tdap vaccine is the "activation of the body's immune system to the effect that immunologically active cells and substances associated with them 'attack' the substance of the spinal cord." Pet. Ex. 8 at 4-5.

To support his theory of molecular mimicry, Dr. Conomy cited to Siegrist,[24] which described generally how vaccines induce immune responses. Pet. Ex. 8.5. Chandra et al. also raised molecular mimicry as a hypothesis for vaccine-induced neuroinflammatory and autoimmune diseases. Pet. Ex. 8.7 at 1. Describing molecular mimicry, Chandra et al. stated "proteins on microbial pathogens are similar to the human proteins and thus induce immune response that damage the human cells." Id.

Because TM is an inflammatory disorder with a suggested autoimmune pathogenesis, Dr. Conomy stated there are some suggestions it can be vaccine-induced. Pet. Ex. 8 at 3-4; see Pet. Ex. 8.7 at 1. For example, Agmon-Levin et al. noted "[t]he pathogenesis of [TM] is mostly of an autoimmune nature, triggered by various environmental factors, including vaccination." Pet. Ex. 8.8 at 1. Agmon-Levin et al. conducted a systematic review of journals published between 1970 and 2009 to analyze cases of TM following vaccination. Id. at 1-2. Their initial search revealed 43 cases, but six were excluded due to insufficient data. Id. at 2. Of the remaining 37 cases, four were reported after diphtheria-tetanus-pertussis ("DTP") or diphtheria and tetanus ("DT") vaccines, and one was reported after a multiple vaccine regimen that included DT. Id. at 2, 3 tbl.1. "In most of these cases[,] the temporal association was between several days and 3 months." Id. at 5. Twenty-seven of the 37 cases (73%) developed symptoms of TM within the first month after vaccination, three developed symptoms between one and two months after vaccination, and seven developed symptoms more than two months after vaccination. Id. at 2, 3 tbl.1. For the cases of TM after DTP and DT, onset was between three and 17 days. Id. at 3 tbl.1.

Agmon-Levin et al. discussed mechanisms by which vaccines may induce TM and noted "molecular mimicry between infectious antigens and self-antigens is the most common mechanism." Pet. Ex. 8.8 at 4 (emphasis omitted). They added that a "host's response to a vaccine, originally generated to produce protective immunity, is similar to its response to an infectious invasion." Id. The authors concluded that "the temporal association between [] vaccines and TM, and the possible mechanism associating these phenomena cannot be ignored. The rarity of TM makes it a difficult disease to study." Id. at 5.

[24] Claire-Anne Siegrist, Vaccine Immunology, in Plotkin's Vaccines 17 (7th ed. 2018).

Dr. Conomy referenced other instances of TM and related conditions resulting from vaccines described in the literature. Pet. Ex. 8 at 4, 6.[25] For example, Chandra et al. described a case report of a healthy 38-year-old male who developed TM, characterized by weakness of his lower extremities, after receipt of measles-mumps-rubella ("MMR") and influenza vaccinations. Pet. Ex. 8.7 at 1. The authors noted that approximately five cases of TM had been reported following tetanus toxoid ("Td") and DTP vaccinations. Id.

ii. Althen Prongs Two and Three

Dr. Conomy opined that Petitioner's Tdap vaccine caused his TM through the autoimmune mechanism described above. Pet. Ex. 8 at 4 ("All of the clinical evidence regarding [Petitioner] points to an acquired, immune-mediated cause for the damage to his spinal cord.").

First, Dr. Conomy agreed with Petitioner's treating physicians and the other experts that TM was the proper diagnosis. Pet. Ex. 8 at 3. The "configuration of the lesion in his thoracic spinal cord, the presence of inflammatory cells in his [CSF], elevated spinal fluid proteins[,] and the presence of immunophoretic bands of protein [immunoglobulin G ("IgG")] in his [CSF]" support a diagnosis of TM, an "immune-pathological condition." Id. at 4. Because the CSF analysis particularly "connot[es] an immune-mediated, inflammatory condition," Dr. Conomy opined it was the Tdap vaccine that directed this response via molecular mimicry. Id. at 3-4.

Next, Dr. Conomy acknowledged that while TM caused by vaccination often manifests between two weeks and three months post-vaccination, "that latency period should not be taken as a hard and fast rule." Pet. Ex. 8 at 6. He pointed out cases of TM that "occurred in a couple to a few days, not longer," after vaccination. Id. For example, Agmon-Levin et al. documented cases of TM with 3-day, 6-day, 7-day, and 17-day onsets. Pet. Ex. 8.8 at 3 tbl.1. Thus, Dr. Conomy suggested Petitioner's onset was a matter of days.[26] Pet. Ex. 8 at 2, 5-6.

Moreover, Dr. Conomy noted "the absence of the identification of any other causal factor in spite of an assiduous search for such." Pet. Ex. 8 at 5. He explained other causes of TM include bacterial infections, viral diseases, multiple sclerosis ("MS"), malignancies, and vascular

[25] In addition to Agmon-Levin et al. and Chandra et al., Dr. Conomy also cited an article by Kulenkampff et. al., but it was published in 1974, and does not reflect the most up-to-date and relevant data. Pet. Ex. 8.9 (M. Kulenkampff et al., Neurological Complications of Pertussis Inoculation, 49 Archives Disease Childhood 46 (1974) (describing neurological complications following DPT vaccine)).

[26] Dr. Conomy did not opine as to a specific date of onset, but it appears he suggested May 24, 2014 (the day Petitioner presented to the ED) as the likely onset. See Pet. Ex. 8 at 2, 4-6; Resp. Ex. C at 4.

disorders. Id. at 3; see Pet. Ex. 8.1;[27] Pet. Ex. 8.3.[28] However, Dr. Conomy reasoned that Petitioner "underwent extensive testing for these disorders by history, examination, imaging studies, [CSF] examination, and numerous blood tests" but they were unrevealing. Pet. Ex. 8 at 3.

2. Petitioner's Expert, Dr. Maria Chen[29]

a. Background and Qualifications

Dr. Chen is a board-certified neurologist. Pet. Ex. 19 at 1. Dr. Chen received a Ph.D. in molecular virology and M.D. from the University of Pennsylvania School of Medicine. Id.; Pet. Ex. 19.11 at 1. As a licensed physician, Dr. Chen actively sees over 2,000 patients per year. Pet. Ex. 19 at 1. She has seen over 100 patients in her career with "some form of [TM]." Id. Dr. Chen is an assistant professor of clinical neurology at the Perlman School of Medicine at the University of Pennsylvania. Id. She also supervises neurology residents and medical students at the University of Pennsylvania Hospital and the Penn Presbyterian Hospital. Id. While she does not currently conduct research, she has authored publications "outlining the mechanisms that viruses, specifically HIV, injure the nervous system." Id. at 1-2; Pet. Ex. 19.11 at 2.

b. Opinion

Dr. Chen opined that Petitioner's Tdap vaccine caused his TM through an allergy or hypersensitivity immune response. Pet. Ex. 23 at 1. She focused her reports on how TM can manifest within 24 hours of vaccination through this proposed theory. Pet. Ex. 19 at 1.

i. Althen Prong One

Dr. Chen proposed that TM can be mediated through an allergy and innate response within 24 hours of vaccine administration. Pet. Ex. 19 at 1. The specific allergic response Dr. Chen focused on was a hypersensitivity response to drugs or antigens. Id. at 2.

Dr. Chen explained that one mechanism of a hypersensitivity response is "that the drug or antigen is taken up by antigen present[ing] cells such as dendritic cells. Antigen presenting cells then process and present the antigen to T and B-cells resulting in production of [immunoglobulin E ("IgE")] antibodies." Pet. Ex. 19 at 2. Then, on future exposure, "the drug or another similar product to the drug (for cross-reactive drugs) is recognized by IgE antibodies resulting in crosslinking of IgE. The crossed-linked IgE can then bind to its receptor [] cells of the innate

[27] Timothy W. West, Transverse Myelitis – A Review of the Presentation, Diagnosis, and Initial Management, 88 Discovery Med. 167 (2013).

[28] Oded Abramsky & Dvora Teitelbaum, The Autoimmune Features of Acute Transverse Myelopathy, 2 Annals Neurology 36 (1977).

[29] Dr. Chen submitted two expert reports in this matter. Pet. Exs. 19, 23. She did not testify at the hearing.

immune response such as mast cells." Id. Once mast cells are activated, their "chemical mediators cause increase in permeability of capillaries allowing for increase access of immune cells and immune compounds into tissue." Id. Importantly, Dr. Chen noted that "[c]ells of the innate immune system such as neutrophils and mast cells have been found in central nervous system [("CNS")] tissue of [neuromyelitis optica ("NMO")] and [MS] hence implicating the innate immune system in autoimmune [CNS] diseases." Id. at 3; see also Pet. Ex. 19.10 at 1;[30] Pet. Ex. 23 at 3.

Dr. Chen clarified that when a hypersensitivity immune response is mediated via IgE, "the IgE is existing from a *prior* immune response." Pet. Ex. 23 at 1. For example, the introduction of the Tdap vaccine "causes cross-linking of existing IgE and this incites a new immune response. Pre-existing IgE can bind to its originally intended antigen or unintended antigens which bear similar characteristics (i.e. cross-react)." Id. Then, "[o]nce bound to the target antigen, the IgE-antigen complex binds and activates mast cells and basophils which express the IgE receptor. These effector cells then release a multitude of other chemical mediates to cause an immune response characterized by an immediate hypersensitivity response." Id.

Because IgE are already present, Dr. Chen explained "the immune response to the administration of the Tdap vaccine is immediate and hence, occurs within a day of administration of the Tdap vaccine." Pet. Ex. 23 at 1. Citing Stone et al.,[31] she stated that the hypersensitivity reactions can occur rapidly within minutes to hours of exposure. Pet. Ex. 19 at 2 (citing Pet. Ex. 19.3 at 1). "Immunological mechanisms can be dependent on the presence of IgE, in which case reactions tend to start rapidly after exposure. Alternatively, they may be independent of IgE, in which case they can occur either rapidly or after many hours, particularly if the mechanism is T-cell mediated." Pet. Ex. 19.3 at 2; see also Pet. Ex. 23C at 2 (describing that immunologically mediated allergic reactions can be delayed and occur within hours or days after exposure).[32]

To support her contention that an allergic mechanism can result in immunological CNS injuries, Dr. Chen referred to a case of a rare form of TM called atopic myelitis, or atopic TM, reported in Asia. Pet. Ex. 19 at 2; see Pet. Ex. 19.1;[33] Pet. Ex. 19.2.[34] Atopic TM is defined as a

[30] Richard M. Ransohoff & Melissa A. Brown, Innate Immunity in the Central Nervous System, 122 J. Clinical Investigation 1164 (2012).

[31] Shelley F. Stone et al., Immediate-Type Hypersensitivity Drug Reactions, 78 Brit. J. Clinical Pharmacology 1 (2013).

[32] Michael M. McNeil & Frank DeStefano, Vaccine-Associated Hypersensitivity, 141 J. Allergy Clinical Immunology 463 (2018).

[33] FA Fasola & OW Aworanti, Hypereosinophilic Atopic Transverse Myelitis, 21 Nigerian J. Clinical Prac. 816 (2018).

[34] Jun-ichi Kira, Atopy and Neural Damage, 41 Internal Med. 169 (2002).

localized myelitis in individuals with elevated levels of IgE, which in turn, implicates an allergy mediated pathway of immune disease. Pet. Ex. 19.1 at 3; Pet. Ex. 19 at 2. "Pathological evaluation by sampling of the spinal cord tissue has indicated that an immune cell of the innate immune system call[ed] the eosinophil is directly involved in the immune mediated injury of the [TM]." Pet. Ex. 19 at 2 (citing Pet. Ex. 19.2 at 2). Dr. Chen opined this example demonstrates that an adaptive immune response via T-cells and B-cells is not the only mechanism by which TM can be mediated. Pet. Ex. 23 at 2.

To support her opinion that an allergy or hypersensitivity reaction is a recognized mechanism for vaccine-associated adverse events, Dr. Chen cited an article by McNeil and DeStefano, which discussed the "types of immunologically mediated hypersensitivity that can occur after vaccination." Pet. Ex. 23C at 2; see Pet. Ex. 23 at 1. However, in contrast to Dr. Chen's explanation, the authors noted that "[v]accine antigens themselves rarely, if ever, are the cause of hypersensitivity reactions. Rather, hypersensitivity reactions after vaccination are usually due to individual vaccine components" such as adjuvants.[35] Pet. Ex. 23C at 3. The authors noted that "[n]o immediate hypersensitivity reactions have been documented" for aluminum-containing adjuvants, the most widely used adjuvants in vaccines, including the Tdap vaccine.[36] Id. at 4. Although Dr. Chen identified aluminum phosphate as an adjuvant in Tdap, she did not explain how it could cause TM given her theory here.

Next, Dr. Chen pointed to anaphylaxis,[37] or anaphylactic shock, to support an allergy or hypersensitivity reaction as a recognized mechanism for vaccine-related adverse events. Pet. Ex. 23 at 1-2. Notably, she noted that anaphylaxis is a Table injury for vaccines containing Td, including Tdap, in the Vaccine Program. Pet. Ex. 23D at 1. Dr. Chen expressed that if the Vaccine Program "recognizes and accepts hypersensitivity reaction in its severe form of anaphylaxis as a[] Table injury, it is not clear why less severe hypersensitivity reactions are not plausible as a[] vaccine-related adverse reaction," particularly "if no other immune trigger has been identified in causing the [TM] which almost always has an immune-mediated cause." Pet. Ex. 23 at 2.

While Dr. Chen opined that TM can be mediated through a hypersensitivity response, she also agreed with Dr. Gershwin's innate immune response theory, as discussed below. Pet. Ex. 23 at 3. She averred that "Dr. Gershwin's theory of an innate immune response does not contradict

[35] "Adjuvants are incorporated into some vaccine formulations to enhance or direct the immune response of the vaccinated subject, specifically to boost T-cell immunity and increase helper T-cell function." Pet. Ex. 23C at 4.

[36] Petitioner received the Adacel Tdap vaccine, which contained an aluminum phosphate adjuvant. Pet. Ex. 1 at 5; Resp. Ex. 31 (package insert); Pet. Ex. 19 at 3.

[37] Anaphylaxis is "a type I hypersensitivity reaction in which exposure of a sensitized individual to a specific antigen [] results in" rash and swelling, followed by respiratory distress. Anaphylaxis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=2577 (last visited Feb. 1, 2023).

nor exclude [her] proposed mechanism of a hypersensitive immune response," and instead, could even "complement" it. Id.

ii. Althen Prongs Two and Three

Dr. Chen agreed with Petitioner's treating physicians and the other experts that Petitioner's diagnosis is TM. Pet. Ex. 19 at 3.

Dr. Chen opined that "[a]utoreactive IgE present in [Petitioner] and responding to the Tdap vaccine is a reasonable mechanism of autoimmunity," as described above. Pet. Ex. 23 at 2. And "[g]iven that components of the [Tdap] (Adacel) vaccine have been demonstrated to activate components of the innate immune response," and "how rapid hypersensitivity responses can occur, . . . it is plausible that the Tdap vaccination cause[d] symptom onset of [TM] in [Petitioner] to be within 24 hours." Pet. Ex. 19 at 1; Pet. Ex. 23 at 2.

3. Petitioner's Expert, Dr. Lawrence Steinman[38]

a. Background and Qualifications

Dr. Steinman is a board-certified neurologist and has practiced neurology at Stanford University for over 40 years. Pet. Ex. 25 at 2; Pet. Ex. 26 at 1. He received his M.D. from Harvard University. Pet. Ex. 26 at 1. Dr. Steinman is currently a professor in the Department of Neurology at Stanford University. Id. He is also "actively involved in patient care" and has cared for hundreds of adults and children with various inflammatory neuropathies, including TM. Pet. Ex. 25 at 2; see also Tr. 49-50. Dr. Steinman has authored or co-authored over 500 publications on immunology. Pet. Ex. 26 at 5-47; Tr. 47.

b. Opinion

Dr. Steinman opined Petitioner developed TM as a result of the Tdap vaccine through the mechanism of molecular mimicry. Pet. Ex. 25 at 6-7. Additionally, he opined onset was 48-72 hours post-vaccination, although his theory would "cover even 24 hours" if one attributed Petitioner's descriptions of foot stiffness as the initial manifestation of TM. Id. at 6.

i. Althen Prong One

Dr. Steinman proposed molecular mimicry to explain how the Tdap vaccine can cause TM. Pet. Ex. 25 at 6. Specifically, he opined that the pertussis component of Adacel (the Tdap vaccine Petitioner received) "contains a molecular mimic of sufficient homology with an antigen MOG (myelin oligodendrocyte [glyco]protein) that is attacked in [TM]" so as to cause an immune response to an otherwise susceptible recipient. Id. at 6, 12; see also Tr. 56.

[38] Dr. Steinman submitted one expert report and testified at the hearing on March 15 and 16, 2022. Pet. Ex. 25; Tr. 44, 349.

Regarding molecular mimicry generally, Dr. Steinman explained that shared structures on a virus, bacteria, or vaccine ("non-self" or "foreign" antigens) can trigger a cross-reactive response to oneself. Pet. Ex. 25 at 7; Tr. 104. "In some people, . . . a foreign antigen may resemble antigen produced by the body. Such molecular mimicry provokes the T cells to attack the body tissues that contain the self-antigens." Pet. Ex. 36 at 4.[39]

More specifically, Dr. Steinman opined that a protein in the vaccine cross-reacted with a protein in the nervous system (MOG), which can cause TM. Tr. 56. He referenced an article by Jarius et al.,[40] which reported that MOG-IgG was found in serum of some patients with optic neuritis and/or myelitis. Pet. Ex. 29 at 1-2. Thirteen percent (6/45) of patients with longitudinally extensive TM (like Petitioner's) were positive for MOG-IgG. Id. The authors postulated that MOG- IgG antibodies may play a pathogenic role in disease. Id. at 10-12.

Dr. Steinman used a three-step process to identify protein sequences that could implicate molecular mimicry. Tr. 58-59. First, he researched the components of the Adacel (Tdap) vaccine and the components of the pertussis toxin. Pet. Ex. 25 at 7. Next, Dr. Steinman conducted a BLAST[41] search to determine whether there was sequence homology between the pertussis toxin and MOG.[42] Id. at 7-8. He found a pertussis toxin sequence and a MOG sequence "with 5 identical amino acids in a stretch of 12 consecutive amino acids."[43] Id. at 8.

Relying on medical literature, Dr. Steinman opined the sequence he found was significant due to the presence of five identical amino acids in a longer sequence. Pet. Ex. 25 at 7. Root-Bernstein[44] found that "[s]imilarities were considered to be significant if a sequence contained at

[39] Lawrence Steinman, Autoimmune Disease, 269 Sci. Am. 107 (1993).

[40] Sven Jarius et al., MOG-IgG in NMO and Related Disorders; A Multicenter Study of 50 Patients. Part 1: Frequency, Syndrome Specificity, Influence of Disease Activity, Long-Term Course, Association with AQP4-IgG, and Origin, 13 J. Neuroinflammation 279 (2016).

[41] A BLAST (Basic Local Alignment Search Tool) search "finds regions of similarity between biological sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance." BLAST, https://blast.ncbi.nlm.nih.gov/Blast.cgi (last visited Mar. 28, 2023).

[42] For a complete explanation of Dr. Steinman's investigation, including his discussion on the number of amino acids required for homology relevant to molecular mimicry as well as the procedure he followed in conducting his BLAST searches, see Pet. Ex. 25 at 8-10.

[43] The five identical amino acids Dr. Steinman identified were GGDPG, with GGVIKDGTPGG as the pertussis epitope and GGLLRDHIPRG as the MOG epitope. Pet. Ex. 25 at 8.

[44] Robert Root-Bernstein, Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Laminin, Collagen IV, CAR, and B1AR As Initial Targets of Disease, 2 Frontiers Pediatrics 1 (2014).

least 5 identical amino acids in 10." Pet. Ex. 40 at 1. Lanz et al.[45] found five out of 12 identical amino acids for molecular mimicry between Epstein-Barr virus and MS. Tr. 66-67; Pet. Ex. 44 at 10. Additionally, papers by Gautam et al. found "5 of 12 amino acids, not even consecutive amino acids, was sufficient to trigger experimental encephalomyelitis (EAE) with involvement of the spinal cord." Pet. Ex. 25 at 7; see also Pet. Ex. 37 at 1;[46] Pet. Ex. 39 at 1;[47] Tr. 63-64. Dr. Steinman explained that there can be an autoimmune response with five out of 12 amino acids. Pet. Ex. 25 at 7 (citing Pet. Ex. 36 at 4); Tr. 64 (explaining the framework needed to be potentially meaningful using the model system in Guatam et al. was five out of 12).

The third step of his process was to search for the pertussis toxin epitope in the Immune Epitope DataBase ("IEDB").[48] Pet. Ex. 25 at 8. The epitope appeared on the IEDB, which Dr. Steinman asserted was evidence that the epitope has been reported in humans. Id. at 9-10; Tr. 353. Dr. Steinman testified that because it was reported in the IEDB, "somebody else studied the region of the pertussis toxin and found it was an epitope or landing pad for parts of the immune system." Tr. 64. Based on this finding, he posited there is "something in the vaccine that has molecular similarities with something that is attacked by the immune system in cases of [TM]." Tr. 64-65. And "[f]inding this mimic in an individual who developed [TM] that shares 5 of 12 identical amino acids with MOG is instructive." Pet. Ex. 25 at 10.

Dr. Steinman acknowledged the limitations to this process of confirming molecular mimicry and sequence homology.[49] On cross-examination, Dr. Steinman conceded that the protein sequence of the pertussis toxin in the vaccine that activated T cells in the MOG are not known. Tr. at 94-95. He also agreed that the epitope he identified in the IEDB was not immunogenic. Tr. 362. Dr. Steinman explained that he could "validate the experiment" and "advance [the] theory closer to certainty" by performing the assays specific to Petitioner in a lab. Pet. Ex. 25 at 10; Tr. 59-60, 65. However, because he is unable to perform research on the

[45] Tobias V. Lanz et al., Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNNA1 and GlialCAM, 603 Nature 321 (2021).

[46] Anand M. Gautam et al., A Polyalanine Peptide with Only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis, 176 J. Experimental Med. 605 (1992). Dr. Steinman is a named author in this paper.

[47] Anand M. Gautam et al., A Viral Peptide with Limited Homology To a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis, 161 J. Immunology 60 (1998). Dr. Steinman is a named author in this paper.

[48] The IEDB "catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes." Immune Epitope Database and Analysis Resource, https://www.iedb.org/ (last updated Mar. 19, 2023). The IDEB is a freely available resource funded by the National Institute of Allergy and Infectious Diseases. Id.

[49] For the limitations acknowledged by Dr. Steinman, see Tr. 93-100.

Petitioner, he asserted that his three-step process, along with supportive medical literature, is the "next best thing." Tr. 59; see also Pet. Ex. 25 at 10.

ii. Althen Prongs Two and Three

Dr. Steinman agreed with the diagnosis of TM and opined "an ingredient in the vaccine cross-reacted with a protein in the nervous system" and "that was, more likely than not, the basis for [Petitioner's TM]." Tr. 53, 56. He stated this was a "primary immune response" since Petitioner had not received an earlier Tdap vaccine nor been infected with pertussis. Pet. Ex. 25 at 11. Dr. Steinman posited this response typically "begin[s] within the first 24 hours of exposure to antigen" but he opined that Petitioner's onset was 48-72 hours post-vaccination. Pet. Ex. 25 at 11-12; see also Tr. 85, 87.

Petitioner received his first Tdap vaccine (Adacel) on May 20, 2014. Pet. Ex. 25 at 5 (citing Pet. Ex. 11 at 1). The next night (May 21), Petitioner noticed foot stiffness before going to bed. The following day (May 22), he noticed numbness and stiffness in his feet and legs which "intensified on May 23." Id. On May 23, he began experiencing "lower back pain and difficulty walking," and by evening, Petitioner could not urinate entirely. Pet. Ex. 2 at 28; see id. By May 24, Petitioner's lower extremity weakness and numbness worsened, and he presented to the ED. Pet. Ex. 25 at 5 (citing Pet. Ex. 11 at 1).

While Dr. Steinman believed the "clear onset" of Petitioner's TM was 48 to 72 hours after vaccination, he acknowledged that Petitioner reported foot stiffness that occurred earlier than 48 hours. Pet. Ex. 25 at 11. Dr. Steinman, however, believed the "foot stiffness" was not related to Petitioner's TM, although he agreed that it could have been a "harbinger" of the illness. Id.; Tr. 114. If it was, Dr. Steinman opined that onset would still fit his theory, because some references recognize an early response (consistent with an immunoglobulin M ("IgM") response) which begins within the first 24 hours of exposure to an antigen. Pet. Ex. 25 at 11; Tr. 85, 87, 103-04.

Dr. Steinman initially opined that Petitioner's CSF showed clonal-like antibody responses of the IgM type (IgM antibodies) early in his diagnosis. Pet. Ex. 25 at 11; Tr. 79. However, on cross-examination, after reviewing Petitioner's CSF results, he acknowledged that instead of IgM antibodies, Petitioner had oligoclonal bands indicating an IgG response. Tr. 110-112. He agreed that IgM antibodies form first and IgG antibodies usually form between a week or two weeks after exposure to an antigen. Tr. 112. However, in his case, Dr. Steinman placed onset between 48 and 72 hours post-vaccination. Tr. 85, 87; Pet. Ex. 25 at 2, 12.

Further, Dr. Steinman testified that determining the initial manifestation of TM is "a matter of interpretation." Tr. 114. For example, onset can be "the first potential sign, . . . the first definite sign, or . . . when diagnosis is made." Id. Given Petitioner's presentation, he opined that onset was 48 to 72 hours post-vaccination. Id. He believed that Petitioner's medical records have some inconsistencies related to onset and symptom progression, and thus, he is "more comfortable" placing onset on the day that Petitioner began having back pain instead of when he experienced only foot stiffness. Tr. 115. Dr. Steinman testified, however, that even if

onset was earlier, it would still be acceptable as that would be a manifestation of the IgM response, which is "very important in this disease." Tr. 114-15.

Ultimately, Dr. Steinman concluded Petitioner's "foot stiffness" or "sensation in the foot" is "not determinative one way or the other." Tr. 364; Pet. Ex. 25 at 6. He placed onset of Petitioner's TM at 48-72 hours post-immunization.[50] Tr. 87; Pet. Ex. 25 at 6. He emphasized that Petitioner had oligoclonal bands four days after vaccination, which indicated a "very notable immune response [was] going on within his brain compartment" that lead to TM. Tr. 365.

Lastly, Dr. Steinman noted he could not find any alternative or non-vaccine factors that could have contributed to Petitioner's TM. Tr. 82.

4. Petitioner's Expert, Dr. M. Eric Gershwin[51]

a. Background and Qualifications

Dr. Gershwin is board certified in internal medicine, rheumatology, and allergy and clinical immunology. Pet. Ex. 47 at 1. He completed his M.D. at Stanford University. Id. He currently works in the Division of Rheumatology, Allergy, and Clinical Immunology at the University of California Davis School of Medicine as Director of the Allergy-Clinical Immunology Program and as a professor.[52] Id.; Tr. 119. In this position, he still sees patients. Tr. 120. Dr. Gershwin has held various editor and reviewer positions on medical journals, and has authored or co-authored over 1,000 publications during his career. Pet. Ex. 47 at 3, 5-137.

b. Opinion

Dr. Gershwin opined, more likely than not, that Petitioner's Tdap vaccine caused him to develop TM through an innate immune response (IgM response) and molecular mimicry (IgG response). Tr. 122; Pet. Ex. 11 at 7. "Over time this IgM response would increase and ultimately lead to a class switch to IgG autoantibodies." Pet. Ex. 11 at 7; see also Pet. Ex. 21 at 2; Pet. Ex. 22 at 3. Dr. Gershwin's reports focused on the pathogenesis of TM and how an innate immune response could explain a rapid onset (24 hours) between the Tdap vaccine and the development of TM. Pet. Ex. 18 at 1; Pet. Ex. 21 at 1.

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[50] Although Dr. Steinman placed onset at 48 to 72 hours, he opined that his opinions would cover "even 24 hours if one would attribute the foot stiffness before going to bed on May 21 as a sentinel manifestation of [TM]." Pet. Ex. 25 at 6. He also acknowledged that TM at the levels described in Petitioner's MRI could be consistent with some impairment below the belly button. Tr. 88.

[51] Dr. Gershwin submitted four expert reports in this matter and testified at the hearing on March 15, 2022. Pet. Exs. 11, 18, 21-22; Tr. 118.

[52] At the time Dr. Gershwin authored his expert reports, he was also Chief of this division. Pet. Ex. 47 at 1.

i. **Althen Prong One**

Dr. Gershwin explained that TM is a neurological disorder "causing segmental bilateral acute spinal cord injury as a result of acute inflammation." Pet. Ex. 11 at 2. He added that "symptoms typically develop over several hours and then worsen over one to several days." Id. The "immune response that leads to pathology in [TM] is a loss of tolerance against neuroantigens." Id. at 2, 6. And because inflammation is a "critical component" of TM, the underlying mechanism "would take the form of either autoantibodies or cytotoxic T cells." Id. at 6.

According to Dr. Gershwin, an innate immune response could explain, among other things, a rapid onset between the Tdap vaccine and the development of TM. Pet. Ex. 21 at 1. Important to Dr. Gershwin's theory is that "one cannot have an adaptive immune response without an innate immune response." Id. at 1; see also Pet. Ex. 18 at 1 ("An adaptive immune response, whether it's a normal response or an autoimmune response, initially requires an innate immune response." (citing Pet. Ex. 18.1));[53] Pet. Ex. 22 at 2 ("[T]he innate immune system always precedes an adaptive response." (citing Pet. Ex. 22A)).[54]

Further, he opined that the innate immune response can cause neurological symptoms. Tr. 135-36. In short, Dr. Gershwin averred a vaccine can cause a rapid release of cytokines and other mediators upon administration. Pet. Ex. 22 at 2. The mediators, which peak 24 hours after vaccination, go from the lymph node to the blood and then to the brain, and produce an inflammatory response. Id.; Pet. Ex. 21 at 2 (explaining an innate response, consisting of antigen presenting cells, is "capable of intense proinflammatory cytokine production" and thus "begin[s] not only the initial injury via inflammation but also initiate[s] the subsequent adaptive (and sustained) immune response"). Dr. Gershwin offered a detailed discussion breaking down the process of the innate immune system involving IgM autoantibodies, local pathology, and the rapid occurrence of this mechanism. See Pet. Ex. 11 at 7.

First, he explained the initial response to vaccination is the activation of preformed IgM autoantibodies. Dr. Gershwin testified that IgM autoantibodies act as "first responder[s]" and are "naturally occurring." Tr. 141; see also Pet. Ex. 11 at 7 (citing Pet. Ex. 11.78 at 1) ("[H]uman anti-GM IgM antibodies are found in the normal antibody repertoire and detected even at one month of age.").[55] Preformed IgMs are those naturally occurring IgMs that mature and are part of the immune response—that is they "expand upon antigen stimulation." Tr. 141. The preformed IgMs will recognize and cross-react with vaccine antigens and produce inflammation.

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[53] Basic Concepts in Immunology, in Immunobiology: The Immune System in Health and Disease 13 (Charles A Janeway et al. eds., 5th ed. 2001).

[54] Douglas M Herrin, Comparison of Adaptive and Innate Immune Responses Induced by Licensed Vaccines for Human Papillomavirus, 10 Hum. Vaccines & Immunotherapeutics 3446 (2014).

[55] María E. Alaniz, Normally Occurring Human Anti-GM1 Immunoglobulin M Antibodies and the Immune Response to Bacteria, 72 Infection & Immunity 2148 (2004).

Tr. 135. He noted "IgM can either be [] in resident cells or translocate within the CNS." Tr. 150; see also Tr. 133 ("IgM could be produced locally. In addition, . . . IgM can get into the CNS through transcytosis.").[56]

During the hearing, Dr. Gershwin referenced Hervé et al.[57] to explain "how vaccines produce reactions." Tr. 130. "Vaccine antigens and immune enhancers (as adjuvants) injected into the muscle are [recognized] by the body as potential pathogens and/or danger signals." Pet. Ex. 22B at 3 fig.1. This "leads to the stimulation of local cells, followed by the recruitment of blood immune cells to the local site and the production of different soluble factors including vasodilators and cytokines, which may trigger the development of signs and symptoms of local inflammation." Pet. Ex. 22B at 3 fig.1.

The cross-reactivity of IgM-producing cells initially leads to local cell stimulation "within the regional lymph nodes adjacent to the injection" and occurs "quite rapidly." Pet. Ex. 22 at 2; see also Tr. 135 ("There will be bystander cells that get activated, and they will lead to tissue damage and tissue necrosis."). Hervé et al. also detailed that after vaccination, toll-like receptors ("TLRs") recognize and bind antigens and potential immune enhancers in a vaccine to trigger inflammation. Pet. Ex. 22B at 4 fig.2. "Resident immune cells, mast cells, monocytes[,] and macrophages are activated within minutes of injection and release soluble factors," such as proinflammatory cytokines, that "allow cell recruitment from blood." Id.

"Once stimulated, the immune system sets off a complex series of innate immune events" such as "release of inflammatory mediators including chemokines and cytokines, activation of complement, and cellular recruitment." Pet. Ex. 22B at 2. The produced cytokines "act both locally . . . and may act systemically at distant organs." Id. at 4 fig.2. The "newly recruited immune cells, mainly composed of blood-born neutrophils, monocytes[,] and T lymphocytes, also contribute to pain sensation by releasing soluble factors, such as cytokines, . . . that can directly interact with local sensory receptors." Id. "These cells will then drain to regional lymph nodes and traffic throughout the body" in addition to the "passage or production of cytokines throughout the body." Pet. Ex. 22 at 2 (citing Pet. Ex. 22B at 2-3). "Several immune-to-brain signaling pathways may propagate an inflammatory response to the [CNS] after peripheral activation of the innate immune system . . . leading to the development of fever and sickness [behaviors]." Pet. Ex. 22B at 4 fig.2. Thus, Dr. Gershwin opined "the innate immune system is an active and viable immune pathway, not only in the local lymph nodes, but potentially throughout the body." Pet. Ex. 22 at 3.

[56] Transcytosis is "a means of transporting a substance across a cell, occurring mainly in sheets of polarized epithelial cells: the substance is taken up by endocytosis, . . . and delivered to the opposite side of the cell where it is released by exocytosis." Transcytosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=50594 (last visited Mar. 21, 2023).

[57] Caroline Hervé et al., The How's and What's of Vaccine Reactogenicity, 39 NPJ Vaccines 1 (2019).

In all, Dr. Gershwin opined "the immune system can become activated extremely rapidly" and this initial innate immune response "can occur within a time interval of 24-36 hours." Pet. Ex. 18 at 1; see also Pet. Ex. 11 at 7. Then, "[o]ver time this IgM response would increase and ultimately lead to a class switch to IgG autoantibodies." Pet. Ex. 11 at 7.

Dr. Gershwin stated, "the immune system can become activated extremely rapidly" and "[a]ctivation of innate immune cells can certainly occur well before 24 hours." Pet. Ex. 18 at 1; Pet. Ex. 22 at 3 (citing Pet. Ex. 22A at 1).[58] "In the case of memory CD8 T cells, they are programmed within the first 24 hours of priming." Pet. Ex. 18 at 1 (citing Pet. Ex. 18.3;[59] Pet. Ex. 18.4).[60] Because IgM is naturally occurring, he posited "a brisk IgM response would be expected and would occur more rapidly." Pet. Ex. 11 at 7 (citing Pet. Ex. 11.78 at 1). For example, in a study with mice, these first responder or innate immune cells were "readily found as early as three hours after immunization." Pet. Ex. 22 at 2 (citing Pet. Ex. 22B at 3).

To support his position, Dr. Gershwin noted there is considerable literature on vaccines and TM. Pet. Ex. 11 at 4-5. Like Dr. Conomy, he cited Agmon-Levin et al., which reported 37 cases of TM associated with different vaccines including Tdap. Pet. Ex. 11 at 4 (citing Pet. Ex. 8.8 at 1). Of those, four cases of TM were associated with Tdap vaccines and presented onset of symptoms within days. Pet. Ex. 8.8 at 4, 3 tbl.1. In addition, Dr. Gershwin cited Riel-Romero[61] which described a case of a patient who developed TM after DTaP vaccination. Pet. Ex. 11.35 at 1. He acknowledged literature did not suggest an association between the Tdap vaccine and TM based on epidemiology. Pet. Ex. 11 at 5. But he noted TM is rare and therefore epidemiological evidence is less important than case reports. Id.; Tr. 146-48.

Dr. Gershwin disagreed with Petitioner's expert's Dr. Chen's proposed theory and argued there is "no evidence that IgE mediates any autoimmune disease." Pet. Ex. 21 at 2.

ii. Althen Prong Two

Dr. Gershwin opined "the initial pathology of TM suffered by [Petitioner] was due to an innate immune response that was activated by circulating cytokines and prostaglandins, [] including trafficking of mononuclear cells within lymphatic circulation." Pet. Ex. 22 at 3; see also Pet. Ex. 21 at 2 ("[A]n innate first response would be a plausible, more likely than not,

[58] Douglas M. Herrin et al., Comparison of Adaptive and Innate Immune Response Induced by Licensed Vaccines for Human Papillomavirus, 10 Hum. Vaccines & Immunotherapeutics 3446 (2014).

[59] Reinhard Obst, The Timing of T Cell Priming and Cycling, 6 Frontiers Immunology 563 (2015).

[60] Sarah E. Henrickson et al., Antigen Availability Determines CD8+ T Cell-Dendritic Cell Interaction Kinetics and Memory Fate Decisions, 39 J. Immunity 496 (2013).

[61] RMS Riel-Romero, Acute Transverse Myelitis in a 7-Month-Old Boy After Diphtheria-Tetanus-Pertussis Immunization, 44 Spinal Cord 688 (2006).

explanation for [Petitioner's] [TM]."). This was Petitioner's first Tdap vaccine, and Dr. Gershwin observed that "he is somewhat unusual in that he is [] immunologically naïve to Tdap as an adult." Pet. Ex. 11 at 7. Because Petitioner had not received the Tdap vaccine before, Petitioner's "first response to the vaccine would be an innate response." Pet. Ex. 21 at 2.

Regarding alternative causes, Dr. Gershwin opined there was no evidence of vascular or infectious causes for Petitioner's TM. Pet. Ex. 21 at 1. Further, no environmental etiology was found. Pet. Ex. 11 at 7. Accordingly, Dr. Gershwin concluded the development of Petitioner's TM was "consistent with the vaccination as the immunological challenge." Id. He acknowledged Petitioner's response was "more rapid than most patients," but maintained that "there is absence of an otherwise explicable etiology and that the nature of the immune response makes an onset such as this case plausible." Pet. Ex. 18 at 2; see also Pet. Ex. 21 at 1-2; Pet. Ex. 22 at 3.

iii. Althen Prong Three

In general, Dr. Gershwin stated acute TM symptoms can "typically develop over several hours and then worsen over one to several days." Pet. Ex. 11 at 2. One of the diagnostic criteria of TM includes progression to nadir between 4 hours and 21 days. Pet. Ex. 18 at 1; Pet. Ex. 11.5 at 2 tbl.1, 3. Dr. Gershwin opined an innate immune response can explain the "rapid onset" of TM in Petitioner. Pet. Ex. 11 at 7; Pet. Ex. 21 at 1-2; Pet. Ex. 22 at 3; Tr. 132.

In his four expert reports, Dr. Gershwin consistently opined Petitioner's onset was approximately 24 hours after vaccination. Pet. Ex. 11 at 7; Pet. Ex. 18 at 1; Pet. Ex. 21 at 2; Pet. Ex. 22 at 1. However, at the hearing, after listening to Petitioner's testimony as well as Dr. Steinman's testimony, Dr. Gershwin testified Petitioner's onset was "more likely" 48-72 hours after vaccination. Tr. 125. He admitted his opinion about onset at the hearing differed from what was in his reports. Tr. 142. He reasoned, however, that he is not a neurologist, and thus, he was not aware of the relevant physiology, specifically "that the foot is innervated by a totally different mechanism or a totally different dermatome distribution than the thoracic spine." Tr. 142. Further, he testified "it's very possible that the stiffness had nothing whatsoever to do with the onset of the [TM]" and "was an incidental complaint secondary to a normal response to a first vaccination." Tr. 123. Ultimately, Dr. Gershwin concluded the "stiffness in the foot [was] probably a red herring." Tr. 134.

Nonetheless, he testified that his theory provides a logical explanation for an onset of 24-48 hours in addition to an onset of 48-72 hours, as described by Dr. Steinman. Tr. 125. In summary, Dr. Gershwin opined that if the pathogenic mechanism is entirely IgM, an onset of 24 hours would be appropriate, and if innate lymphoid cells are also involved, an onset of 48-72 hours would be appropriate, but would also be "compatible" with 24-48 hours. Tr. 127-28, 132.

5. Respondent's Expert, Dr. Jeffrey Gelfand[62]

[62] Dr. Gelfand submitted two expert reports in this matter and testified at the hearing on March 15, 2022. Resp. Exs. A, F; Tr. 154.

a. Background and Qualifications

Dr. Gelfand is a board-certified neurologist. Resp. Ex. A at 1. Dr. Gelfand completed his M.D. at Harvard Medical School. Id. at 2; Resp. Ex. H at 1. He is currently an Associate Professor of Clinical Neurology and an attending neurologist at the University of California at San Francisco, as well as director of the MS Neuroimmunology Fellowship Program. Resp. Ex. A at 1-2; Resp. Ex. H at 2; Tr. 155-56. Dr. Gelfand's practice involves diagnosing patients with demyelinating conditions including TM. Tr. 159. His clinical research and active practice focus on neuroinflammatory disorders, including TM. Resp. Ex. A at 2; Resp. Ex. H at 3, 19; Tr. 157. Dr. Gelfand has published articles in this area and is involved in the editorial process of peer-reviewed journals. Tr. 156-57; Resp. Ex. H at 21-31.

b. Opinion

Dr. Gelfand opined that Petitioner suffered from acute TM but that it was "unrelated to the Tdap vaccine administered less than 48 hours before clinical onset of the myelitis." Resp. Ex. A at 6; see also Tr. 206-07.

i. Althen Prong One

Dr. Gelfand took issue with the proposed mechanism of molecular mimicry. Resp. Ex. A at 4-5. He stated that neither Dr. Conomy nor Dr. Gershwin provided specific evidence about what components in the Tdap vaccine, if any, can "cross-react with antigens in the spinal cord and cause myelitis specifically." Id. at 5. "[M]olecular mimicry is the theory under which an infectious or exogenous agent (such as a protein in the Tdap vaccination) is similar enough to a host antigen that it induces an antigen-specific auto-inflammatory response while evading usual immune tolerance protections against autoimmunity." Id. (citing Resp. Ex. A, Tab 5 at 1).[63] Yet Dr. Gelfand averred that they did not explain "how the Tdap vaccine might mimic a self-protein in the [CNS]." Id. Dr. Gelfand's own review of published scientific literature returned "no clear evidence . . . that antigens in the Tdap vaccine mimic [CNS] antigens." Id.

Moreover, he opined that Dr. Gershwin did "not provide specific evidence of how an IgM response, let alone one specifically provoked by Tdap vaccination, is implicated in the pathogenesis of acute [TM] as a specific disease entity or how a Tdap provoked IgM response can cause [TM]." Resp. Ex. A at 5. Further, Dr. Gelfand testified that while IgM may play a role in the pathogenesis of some types of neuroinflammatory conditions, there are no studies or research that describe any role for IgM in the etiology of neurological symptoms in patients with TM. Tr. 188, 200.

Nonetheless, Dr. Gelfand stated that even if molecular mimicry was postulated, "the time course of a myelitis developing less than 48 hours after Tdap vaccination would be too soon." Resp. Ex. A at 5. He testified that "an immune response to vaccination, particularly with an adaptive immune response like this, would be expected to take several days." Tr. 189.

[63] Lori J. Albert & Robert D. Inman, Molecular Mimicry and Autoimmunity, 341 New Eng. J. Med. 2068 (1999).

He opined Dr. Gershwin did "not provide specific evidence in the medical literature that [TM] can occur as early as 48 hours after Tdap vaccination." Resp. Ex. A at 5. Dr. Gelfand opined "[i]t takes several days, . . . more than five days, for example, to really develop a typical adaptive immune response." Tr. 208. For support, he referenced Baxter et al., which used specific time intervals to measure and compare a possible association of a demyelinating event following vaccination. Tr. 191-92; Resp. Ex. A, Tab 9 at 1. The authors identified five to 28 days as the most likely interval following vaccination to result in a demyelinating illness if one were to occur. Resp. Ex. A, Tab 9 at 3. Dr. Gelfand pointed out at the hearing that the authors "drew a line at two days, at 48 hours, and not at one day or zero days." Tr. 192. Additionally, he cited Langer-Gould et al.,[64] a case-controlled analysis that measured a small increase in risk of a [] demyelinating attack within 14 days of [] vaccine exposure." Resp. Ex. A at 6 (citing Resp. Ex. A, Tab 8). "[N]o single vaccine (including Tdap) was statistically significantly associated with a demyelinating event" and Dr. Gelfand found it notable that "Tdap was one of the most common vaccines administered in the dataset." Id.

Finally, Dr. Gelfand noted medical literature on the association between the Tdap vaccine and TM is rare. Resp. Ex. A at 6. In Agmon-Levin et al., for example, only four published cases were associated with DTP or DT and one case with pertussis. Id. (citing Pet. Ex. 8.8 at 3 tbl.1). Baxter et al. concluded there is "no association between vaccination (including Tdap) and [TM]." Id. (citing Resp. Ex. A, Tab 9 at 1). Dr. Gelfand conducted a search of medical literature from 2009 to 2018 and did not find "any clear additional [] cases of [TM] associated with Tdap." Id. Moreover, he testified he is unaware of any "research exploring a role for IgM directly causing neurologic symptoms associated with [TM]." Tr. 188, 200.

ii. Althen Prong Two

Dr. Gelfand questioned whether there was an alternative diagnosis. He agreed that Petitioner's "MRI is consistent and in this clinical context [] diagnostic of TM that is longitudinally extensive." Tr. 171. Nevertheless, Dr. Gelfand raised NMO spectrum disorder as a "possible more specific cause of longitudinally-extensive myelitis" and that it cannot be formally excluded. Resp. Ex. A at 6. He noted that testing for NMO antibody (aquaporin-4 IgG) "was repeatedly discussed as something to be considered as an outpatient with planned post-acute neurology follow-up, but there is no record of this being sent or resulted in the available record." Id. at 4. Dr. Gelfand opined "this test is important diagnostically as NMO is an important cause of longitudinally extensive myelitis specifically and relapse risk is high after a first myelitis if the NMO antibody is positive." Id. (citing Resp. Ex. A, Tab 4).[65]

Although he questioned whether there was a possibility that Petitioner had NMO spectrum disorder, and raised the importance of NMO antibody testing, Dr. Gelfand did not

[64] Annette Langer-Gould et al., Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases, 71 JAMA Neurology 1506 (2014).

[65] Dean M. Wingerchuk, International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorders, 85 Neurology 177 (2015).

identify any alternative cause for Petitioner's TM by a preponderant evidence standard. Instead, he agreed that Petitioner had "idiopathic acute [TM]," meaning there is no specifically identified cause, but the illness is still considered to be inflammatory in nature. Tr. 206.

iii. Althen Prong Three

Dr. Gelfand asserted that the first ED notes support that "Petitioner had symptoms that had been worsening over a three-day period." Tr. 167, 170. On this point, he credited the opinions of Petitioner's treating physicians. Tr. 175-77. Accordingly, Dr. Gelfand disagreed with Dr. Steinman's opinion on onset (48 to 72 hours). Resp. Ex. F at 2. Also, unlike Dr. Steinman and Dr. Gershwin, Dr. Gelfand opined that Petitioner's foot stiffness, starting on May 21, 2014, was the first symptom of TM, and he further opined that this symptom progressed over several days. Id. Dr. Gelfand placed onset between 24 and 48 hours after vaccination. Tr. 169.

He explained "[i]t is very typical [for patients with TM] to have symptoms that start in the feet and then can ascend up until the level of [] the spinal cord injury." Tr. 163. This is because when there is an injury to the spinal cord, it "can affect fibers that control everything from [the level of the injury] downward." Tr. 164. Dr. Gelfand testified that in terms of localization, extensive myelitis from T2 through T9 can present sensory symptoms "from just above the nipple line all the way down to the feet." Tr. 172-75. Thus, he opined "an MRI showing thoracic-level myelitis absolutely can cause lower extremity symptoms, including foot stiffness." Tr. 173; see also Resp. Ex. F at 2.

Petitioner's MRI showed a "long segment of abnormal central cord signal" extending from T2 to T9. Tr. 171 (citing Pet. Ex. 2 at 78). Dr. Gelfand opined "the [foot] stiffness was more likely than not from neuropathic involvement from the spinal cord injury," and he further "interpret[ed] the early findings of stiffness in the feet, which worsened the next day and then worsened more and continued to evolve, to be part of the same spectrum of an evolving spinal cord syndrome rather than something separate or incidental." Tr. 187-88.

Further, the radiologist noted that Petitioner's MRI showed "potential minimal enhancement of the cord at T6 on the sagittal T1 images." Tr. 171 (citing Pet. Ex. 2 at 78). Given the MRI findings, Dr. Gelfand opined that Petitioner's MRI was consistent with and diagnostic of a "longitudinally extensive [TM]." Id. Regarding the potential minimal enhancement seen at the T6 level, Dr. Gelfand explained that "[e]nhancement is a breakdown in the blood-brain barrier . . . often interpreted as a sign of acute inflammation." Id.

Dr. Gelfand reviewed pertinent entries in the medical record which he opined indicated that Petitioner began to develop stiffness in his bilateral lower extremities on Wednesday, May 21, 2014. Tr. 176-78; see Pet. Ex. 2 at 3 ("This past Wednesday [] [Petitioner] began to develop symptoms [] describe[d] as a stiffness in the bilateral lower extremities."); Pet. Ex. 2 at 5 ("[Petitioner] felt that his feet were stiff."); Pet. Ex. 10 at ¶ 5 ("On the night of May 21st . . . [Petitioner] noticed some minor stiffness in [his] feet before [he] went to bed. The following day, [he] experienced some numbness and stiffness in [his] feet and legs."). Dr. Gelfand opined that this "evolution of symptoms is consistent with TM . . . [and] the spectrum of clinical

symptoms [is] a continuum and [] part of this same evolving neurologic process" and not "something separate or incidental." Tr. 178, 188.

Dr. Gelfand cited Baxter et al. for the time intervals and compared a possible association of a demyelinating event following vaccination. Tr. 191-92 (citing Resp. Ex. A, Tab 9 at 1). In Baxter et al., the authors identified a range of five to 28 days as the most likely interval following vaccination for onset of a demyelinating illness. Resp. Ex. A, Tab 9 at 3. However, they also used a second risk window of two to 42 days to ensure that they did not miss any cases. Id. Dr. Gelfand acknowledged this secondary risk window at the hearing when he testified that the Baxter et al. authors "drew a line at two days, at 48 hours, and not at one day or zero days." Tr. 192.

While Dr. Gelfand first opined that onset of an adaptive response required five days, he later testified that it would take "more than five days . . . if not longer." Tr. 208. He concluded that "24 hours to 48 hours is very fast." Id.

In summary, Dr. Gelfand opined that "Petitioner developed acute [TM] with first clinical symptoms 24 to 48 hours following Tdap vaccination but that the . . . evidence does not support the conclusion that the [] vaccination, more likely than not, caused his myelitis." Tr. 206-07.

6. Respondent's Expert, Dr. Thomas Forsthuber[66]

a. Background & Qualifications

Dr. Forsthuber is board certified in anatomical and clinical pathology and has over 25 years of experience in immunology. Resp. Ex. C at 1. Dr. Forsthuber received a Doctor of Medicine[67] in immunology and M.D. at the University of Tübingen in Germany. Resp. Ex. I at 2; Tr. 219. He is licensed to practice medicine in the United States. Resp. Ex. I at 2. Dr. Forsthuber is a Professor of Immunology and Endowed Chair of Biotechnology at the University of Texas at San Antonio and an Adjunct Professor of Pathology and Microbiology & Immunology at the University of Texas Health Sciences Center, San Antonio. Resp. Ex. C at 1. Dr. Forsthuber's research focuses on autoimmune disease and T cell immunology. Id.; Tr. 220. He has published over 100 papers and book chapters relating to immunology and the pathogenic mechanisms of autoimmune diseases. Tr. 220; Resp. Ex. I at 22-39.

b. Opinion

Dr. Forsthuber opined "to a reasonable degree of medical and scientific probability" that the Tdap vaccine was not causally related to Petitioner's neurological condition. Resp. Ex. C at 3, 12.

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[66] Dr. Forsthuber submitted three expert reports in this matter and testified at the hearing on March 16, 2022. Resp. Exs. C, E, G; Tr. 216.

[67] According to Dr. Forsthuber, this is equivalent to a Ph.D. Tr. 219.

i. **Althen Prong One**

Dr. Forsthuber disagreed with Petitioner's proposed theories of hypersensitivity response and molecular mimicry. First, like Dr. Gershwin, Dr. Forsthuber rejected Dr. Chen's allergy or hypersensitivity response. Resp. Ex. E at 1-5. He opined there is "no evidence that 'atopic myelitis' is mediated by 'an innate, allergy response.'" Id. at 3. In fact, Dr. Forsthuber explained that in TM, the CSF shows evidence of abnormalities which are consistent with adaptive immunity and not a hypersensitivity response. Id. In this regard, he seemed to agree that TM involves an adaptive immune response.

While Dr. Forsthuber recognized molecular mimicry as a sound mechanism in some situations, he opined it is not supported here. Resp. Ex. C at 6-10. And he criticized the medical literature cited by Dr. Conomy in support of molecular mimicry. Id. at 4-5. He opined that Chandra et al., Kulenkampff et al., and Agmon-Levin et al. do not provide specific support of a causal role between the Tdap vaccine and TM. Id. Additionally, he pointed out that the Tdap vaccine is not the same as the DTP, DT, or Td vaccines, which were analyzed in those articles.[68] Id. at 5. Moreover, he stated that Kulenkampff et al., discussed neurological convulsions in children to which Dr. Forsthuber opined is irrelevant because "TM is mediated by an autoimmune mechanism, whereas convulsions typically are not." Id. Moreover, the earliest onset reported in Agmon-Levin et al. was three days after DT vaccination and six to 17 days after DTP vaccination. Id. Thus, Dr. Forsthuber opined the literature cited by Dr. Conomy argues "against a role for the Tdap vaccine and the neurological condition of [Petitioner]" and that the onset of TM "slightly over 24 hours after vaccination is not consistent" with Tdap vaccine causation via molecular mimicry.[69] Id.

Next, Dr. Forsthuber rejected Dr. Steinman's three-step process supporting his molecular mimicry theory as "unreliable." Resp. Ex. G at 3, 22-24.[70] He opined that BLAST searches were not designed to identify molecular mimicry. Id. at 14, 23; Tr. 227. Instead, he stated "BLAST [searches] [were] designed to reveal evolutionary relationships rather than immunological ones." Resp. Ex. G at 23; Tr. 245 ("[I]t's not possible to do a BLAST search, compare two proteins with each other and then conclude that a certain similarity is sufficient to induce [a] T cell response.").

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[68] The undersigned agrees that Kulenkampff et al. is an older article, and that the Tdap vaccine was not at issue there. However, in Agmon-Levin et al., the authors stated that "a safer acellular pertussis vaccine (DTaP) was introduced in the US in 1991. Nevertheless, four cases of TM following DT and DTP . . . have been reported since then." Pet. Ex. 8.8 at 4. Thus, it is not clear that Dr. Forsthuber is entirely accurate on this point.

[69] Dr. Forsthuber acknowledged that molecular mimicry has been proposed as a pathogenic mechanism in idiopathic TM. Resp. Ex. C at 3.

[70] For a full and detailed explanation of Dr. Forsthuber's opinions about Dr. Steinman's three-step process, see Resp. Ex. G at 3-29.

Nonetheless, Dr. Forsthuber attempted to replicate Dr. Steinman's findings by performing his own BLAST search for the pertussis toxin and the MOG protein sequence. Resp. Ex. G at 20. His "search yielded the result, 'no significant similarity found.'" Id. Dr. Forsthuber concluded that "the MOG sequence claimed by Dr. Steinman as [a] 'molecular mimic' with pertussis toxin was not contained in the MOG protein sequence reported in the [] database." Id. Therefore, Dr. Forsthuber surmised that Dr. Steinman used an isoform[71] of MOG that "has not been reported in the MS or TM literature as a target of the autoimmune response." Id. (citing Resp. Ex. G, Tab 11).[72] "The version of the MOG protein [] Dr. Steinman used for his BLAST searches [was] significantly longer (295 amino acids) than the conventional MOG (247 amino acids . . .)." Id. He testified that Dr. Steinman used a longer string of amino acids "outside the conventional canonical MOG sequence." Tr. 263. For these reasons, Dr. Forsthuber concluded that the BLAST search did "not reveal molecular mimicry between Tdap and MOG." Resp. Ex. G at 23.

Even if BLAST searches were an effective tool for identifying immunological relationships, Dr. Forsthuber opined that the "insignificant E-values, reveal no meaningful similarity between pertussis toxin and MOG."[73] Resp. Ex. G at 23. He explained E-values measure the degree of meaningful similarity between two proteins. Id. at 14; Tr. 233. He testified an E-value greater than the BLAST cutoff, which is "one times 10 to the minus sixth, meaning 0.000001," indicates there is "no meaningful similarity" between the two compared proteins and that it is just a "random observation." Tr. 233, 235. Dr. Forsthuber found the corresponding BLAST E-value for Dr. Steinman's search was 0.12, indicating "there is no significant sequence similarity." Resp. Ex. G at 17, 16 fig.7. He added that "the E-value of Dr. Steinman's sequence [] is in the same range as that of E-values of proteins not implicated in molecular mimicry." Id. But "no matter how significant the E-values are," Dr. Forsthuber opined "sequence similarities revealed by BLAST or LALIGN[74] searches cannot provide proof that these sequences will rise to the level of molecular mimicry in humans." Id. at 19. Ultimately, he averred "there is no scientifically accepted method to substantiate whether a particular sequence similarity found by BLAST search would rise to the level of molecular

[71] An isoform refers to "any of two or more functionally similar proteins that have a similar but not an identical amino acid sequence." Isoform, Merriam-Webster, https://www.merriam-webster.com/dictionary/isoform (last visited Mar. 22, 2023). Dr. Forsthuber opined Dr. Steinman used isoform 13. Resp. Ex. G at 20.

[72] Kathrin Schanda, Differential Binding of Antibodies to MOG Isoforms in Inflammatory Demyelinating Diseases, 8 Neurology: Neuroimmunology & Neuroinflammation e1027 (2021).

[73] For a more detailed explanation of Dr. Forsthuber's opinion as to the fact that Dr. Steinman used the wrong MOG protein when performing his BLAST search, see Tr. 262-66.

[74] LALIGN (local alignment tool) "can compare two protein or DNA sequences for local similarity and show the local sequence alignments." Resp. Ex. G at 15 n.11. Dr. Forsthuber refined the BLAST results using the LALIGN tool because "it permits better targeted similarity searches." Id. at 15. He opined that LALIGN, like BLAST, is designed to identify evolutionary relationships, not immunological ones. Id. at 21.

mimicry or have any relationship to the development of a disease process in [a] human." Id. at 11.

Next, Dr. Forsthuber criticized Dr. Steinman's use of Root-Bernstein, Lanz et al., and the Gautam et al. papers as support for the claim that five out of 12 amino acids constitutes meaningful sequence similarities.[75] Resp. Ex. G at 23, 10; Tr. 228-29. For example, Lanz et al. did not use a BLAST search to identify molecular mimicry. Tr. 253-54. And "Gautam et al. did not claim or report a method for identifying molecular mimics based on 'identity of x of y amino acids, not even in sequence.'" Resp. Ex. G at 23. Instead, Gautam et al. investigated a known sequence and showed that specific amino acids need to be in defined positions to react, which is an "entirely different approach" than that used by Dr. Steinman. Id.; Tr. 239-41. Dr. Forsthuber opined these "short regions are so frequent that it's really somewhat questionable whether they play a role in molecular mimicry." Tr. 228-29. For support, he cited Trost et al.[76] and Kanduc et al.,[77] which demonstrated the commonality of sequence similarities, and Silvanovich et al.,[78] which "suggested that homologies based on searches for short amino acid matches of [eight] amino acids or fewer are a product of chance" and "does not amount to 'molecular mimicry.'" Tr. 228-31 (citing Resp. Ex. G, Tabs 1-3); see also Resp. Ex. G at 2, 23. Additionally, he cited Frankild et al.,[79] which "confirmed that central positions of a peptide . . . are important for [T cell receptor] recognition." Resp. Ex. G at 26. He explained that it is "inevitable that BLAST searches will regularly yield amino acids that overlap between proteins simply by chance," and "you can't predict whether a T cell could be activated or not." Id. at 14, 19; Tr. 247.

Regarding Dr. Steinman's use of the IEDB database, Dr. Forsthuber opined was misleading because "[n]either the alleged pertussis toxin epitope [] nor the alleged MOG epitope [] were reported in the IEDB database" at the time he wrote his report. Resp. Ex. G at 24. Dr. Forsthuber stated that Dr. Steinman set the IEDB search parameters "such that similar, but not identical sequences are shown by using the lowest possible stringency setting of 70% for his searches." Id. at 24, 25 fig.12. According to Dr. Forsthuber, these are not the same peptides as the alleged molecular mimic. Id. at 24. He testified this means "an immune response has not been reported by investigators in IEDB specifically against this peptide." Tr. 277. Because it "is

[75] Dr. Forsthuber also opined that Dr. Steinman's "matching 5 amino acids are not consecutive" in the sequence, "but they are spread out over a stretch of 12 amino acids and interspersed with amino acids that do not match." Resp. Ex. G at 14; Tr. 249.

[76] Brett Trost et al., Bacterial Peptides are Intensively Present Throughout the Human Proteome, 1 Self/Nonself 71 (2010).

[77] Darja Kanduc et al., Massive Peptide Sharing Between Viral and Human Proteomes, 29 Peptides 1755 (2008)

[78] Andre Silvanovich et al., The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity, 90 Toxicological Sciences 252 (206).

[79] Sune Frankild et al., Amino Acid Similarity Accounts for T Cell Cross-Reactivity and for "Holes" in the T Cell Repertoire, 3 PLoS ONE e1831 (2008).

only part of much larger peptide, it cannot be predicted if his sequence could have any role in inducing immune responses in these assays." Resp. Ex. G at 25; see also Tr. 228. Lastly, Dr. Forsthuber opined the pertussis toxin epitope does not induce immune responses. Resp. Ex. G at 25 (citing Resp. Ex. G, Tab 13);[80] Tr. 282.

Moving to Petitioner's experts' opinions related to IgM immune responses, Dr. Forsthuber criticized their reliance on Villar et al. because in that paper, the authors described the potential role for IgM in MS but not TM. Resp. Ex. G at 28. Moreover, Dr. Forsthuber asserted that oligoclonal bands are restricted to the CNS whereas the Tdap vaccine "induces IgM antibodies in the lymph nodes draining to the injection site, but not in the CNS." Id. He added, "IgM antibodies in the CNS are associated with abnormal CD5+ B cells," but that the Tdap vaccine "does not induce abnormal CD5+ B cells, and B cells induced by Tdap would not be restricted to the CNS." Id. at 28-29 (citing Pet. Ex. 41).

Regarding the opinions of Dr. Gershwin, Dr. Forsthuber agreed that "the initial innate immune response serves to prime the adaptive immune system." Resp. Ex. E at 9. But he opined that the adaptive immune response "initiates and directs" the innate immune response within the CNS during neuroinflammatory diseases. Id. at 5. Dr. Forsthuber did not agree that TM could be caused without an adaptive immune response. Id. at 5, 8. He opined that the "cells of the innate immune system contribute to [TM], but they do not cause this condition without being first instigated by the adaptive immune system." Id. at 8; see also Resp. Ex. G at 29 ("[W]ithout an adaptive immune response there would be no molecular mimicry and supposedly no TM.").

Dr. Forsthuber outlined key immunological concepts relevant for immune responses after vaccination and concluded "there is no reliable evidence that immune responses to vaccine[s] are initiated within the CNS." Resp. Ex. G at 30-31. "[T]he adaptive immune system . . . recruits cells of the innate immune system to the CNS, where these infiltrating cells ([] monocytes and dendritic cells) and local cells . . . become activated and cause tissue pathology via production of pathogenic mediators (i.e. cytokines, . . .)." Resp. Ex. E at 8.

Next, Dr. Forsthuber opined that "the presence of autoantibodies does not necessarily equate to induction of autoimmune pathology." Resp. Ex. C at 11 (citing Resp. Ex. C, Tab 8).[81] He averred Alaniz et al., referenced by Dr. Gershwin, illustrates this point. Id. (citing Pet. Ex. 11.78 at 1). Importantly, Dr. Forsthuber stated that IgM antibodies do not penetrate the blood-brain barrier. Resp. Ex. C at 11; Resp. Ex. E at 4. He explained that the blood-brain barrier "shields the brain from undesired and potentially toxic molecules and pathogens circulating in the blood stream," thus preventing large proteins or hydrophilic molecules from freely entering

[80] Wolfgang Schmidt & Alexander Schmidt, Mapping of Linear B-Cell Epitopes of the S2 Subunit of Pertussis Toxin, 57 Infection & Immunology 438 (1988).

[81] Eric P. Nagele et al., Natural IgG Autoantibodies Are Abundant and Ubiquitous in Human Sera, and Their Number Is Influenced By Age, Gender, and Disease, 8 PLoS ONE e60726 (2013).

the CSF. Resp. Ex. C at 11 (citing Resp. Ex. C, Tab 10).[82] "In strong contrast, IgM antibodies, which are much larger . . . are usually restricted to blood vessels and essentially do not diffuse into the CSF." Id. (citing Resp. Ex. C, Tab 9).[83] He concluded that "Dr. Gershwin's theory of IgM antibodies as the causative mechanism for inducing TM after Tdap vaccination in [Petitioner] does not apply because these IgM antibodies, even if they existed, do not cross-over from the blood into the CNS." Id. Moreover, Dr. Forsthuber explained that IgM antibodies are generally "directed against lipids" and the "[p]ertussis toxin is not lipid." Tr. 300.

Additionally, Dr. Forsthuber criticized the medical literature Dr. Gershwin used to support his position that the Tdap vaccine induces increased levels of cytokines in the blood. Resp. Ex. G at 31. Talaat et al.,[84] which investigated the flu vaccine not Tdap, found cytokine levels were so low that they "dwarf in comparison" to those observed in heathy, unvaccinated individuals. Id. (citing Pet. Ex. 22C). Dr. Forsthuber offered Kleiner et al.[85] and Lim et al.[86] which found no significant changes in the level of cytokines. Id. at 31-32 (citing Resp. Ex. G, Tabs 17-18).

Lastly, Dr. Forsthuber addressed Dr. Gershwin's reliance on Grigg et al.,[87] which discussed pro-inflammatory T cells (ILC3s) in the CNS and their role in "autoimmune neuroinflammation" relative to the pathogenesis of multiple sclerosis type illnesses. Tr. 307-11; see Pet. Ex. 48 at 1. Dr. Forsthuber explained that the adaptive immune response (acknowledging the timing implications) is required for the recruitment of ILC3 cells to the brain, which then induce neuroinflammation. Tr. 308. He noted several important differences between the Grigg et al. paper and what was suggested by Petitioner's expert. In the Grigg et al. study, the mice that were "immunized with myelin antigen, . . . already ha[d] disease," and then

[82] Guilhem Bousquet & Anne Janin, Passage of Humanized Monoclonal Antibodies Across the Blood-Brain Barrier: Relevance in the Treatment of Cancer Brain Metastases?, 2 J. Applied Biopharmaceutics & Pharmacokinetics 50 (2014).

[83] Edward A. Neuwelt et al., Osmotic Blood-Brain Barrier Opening to IgM Monoclonal Antibody in the Rat, 250 Am. J. Physiology R875 (1986).

[84] Kawsar R. Talaat et al., Rapid Changes in Serum Cytokines and Chemokines in Response to Inactivated Influenza Vaccination, 12 Influenza & Other Respiratory Viruses 202 (2018).

[85] Giulio Kleiner et al., Cytokine Levels in the Serum of Healthy Subjects, 2013 Mediators Inflammation 434010.

[86] Pei Wen Lim et al., Potential Use of Salivary Markers for Longitudinal Monitoring of Inflammatory Immune Responses to Vaccination, 2016 Mediators Inflammation 6958293.

[87] John B. Grigg et al., Antigen-Presenting Innate Lymphoid Cells Orchestrate Neuroinflammation, 600 Nature 707 (2021).

ILC3s were examined 15 days after immunization. Tr. 310. Freund's adjuvant,[88] a very aggressive adjuvant not used in humans, and pertussis toxin were also administered to mice. Tr. 310-11. ILCs were not found in the mice that only received pertussis. Tr. 311. Therefore, Dr. Forsthuber concluded that the paper "disproves the claims that these ILCs have any role in the Tdap vaccination." Id.

ii. Althen Prongs Two and Three

Dr. Forsthuber opined that the development of adaptive autoimmunity takes more than 24 hours and "therefore it is not feasible that the Tdap vaccine caused TM in [Petitioner] in such a short period of time." Resp. Ex. E at 6. He posited Petitioner's onset was "most likely within 24-48 hours after vaccination and not within 48-72 hours;" however, he did not believe that this timeframe was "consistent with TM induced by the Tdap vaccine." Resp. Ex. G at 2, 29; see also Resp. Ex. C at 10; Resp. Ex. E at 8 ("[T]he argument that Tdap induced the rapid onset of symptoms in [Petitioner] via the innate immune system is not logical because the adaptive immune system would have to be activated first.").

Dr. Forsthuber stated it is critical to note that "it takes a certain period of time for the adaptive immune system to initiate and orchestrate [an] attack on the CNS in TM." Resp. Ex. C at 6-7. He opined it can take several days for the adaptive immune system to "mount a proper immune response." Resp. Ex. E at 7. Dr. Forsthuber detailed the sequence of events after vaccination, concluding that "even if the Tdap vaccine could induce autoimmune responses, and there is no evidence for this, it is not feasible that the vaccine could cause Petitioner's TM in 24 hours." Id.; see also Tr. 284-91. Instead, Dr. Forsthuber opined Petitioner's onset "would be much more consistent with an autoimmune process that started at least one to three weeks prior to his clinical manifestations of TM." Resp. Ex. C at 10.

Dr. Forsthuber agreed that there was no alternative cause for Petitioner's TM. Tr. 334-35. However, he noted that "half of TM cases occur spontaneously without any clearly identifiable preceding event." Resp. Ex. C at 6. He therefore dismissed Dr. Conomy's and Dr. Gershwin's argument that the Tdap vaccine had to be the cause of Petitioner's TM because of the lack of reasonable alternatives (i.e., there were no other apparent infectious events). Id. at 3, 6; Tr. 334-35. While it is "unfortunate" that Petitioner developed TM after vaccination, Dr. Forsthuber testified that it is "human nature to associate bad events with each other." Tr. 335.

[88] Freund's adjuvant is "a water-in-oil emulsion incorporating antigen, in the aqueous phase, into lightweight paraffin oil with the aid of an emulsifying agent. On injection, this mixture (Freund incomplete a.) induces strong persistent antibody formation. The addition of killed, dried mycobacteria, e.g., Mycobacterium butyricum, to the oil phase (Freund complete a.) elicits cell-mediated immunity (delayed hypersensitivity), as well as humoral antibody formation." Freund Adjuvant, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=37052 (last visited Mar. 23, 2023).

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley, 991 F.2d at 1575.

Despite the weight afforded to medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) (Section 13(b)(2) "must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them").

C. Causation

To receive compensation through the Program, a petitioner must prove either (1) that he suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that he suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must

show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege he suffered a Table Injury, he must prove a vaccine he received caused his injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d. 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether a petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in his favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

V. ANALYSIS

A. Althen Prong One

Under Althen Prong One, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs.,

98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support his theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner has provided preponderant evidence that the Tdap vaccine can cause TM through the mechanism of molecular mimicry. The hypersensitivity theory and innate immune response theory, however, are not supported by preponderant evidence. The reasons for these findings are described below.

First, as for the mechanistic theory of hypersensitivity, Petitioner offered the opinions of Dr. Chen, who proposed that TM can be mediated through an allergy and hypersensitivity response within 24 hours of vaccine administration. However, Dr. Chen offered no reliable evidence to show that the pathogenesis of TM is a hypersensitivity reaction, or that TM is caused by an IgE immune mediated response. In this regard, the undersigned finds Dr. Gershwin persuasive, and he succinctly explained that there is "no evidence that IgE mediates any autoimmune disease." Pet. Ex. 21 at 2. In summary, there is not scientific support for Dr. Chen's theory, it is not sound or reliable, and there is not preponderant evidence that the Tdap vaccination can cause TM via a hypersensitivity reaction.

The next causal mechanism offered by Petitioner is Dr. Gershwin's theory of an innate immune response, which he offers to explain a rapid onset between the Tdap vaccine and the development of neurological symptoms which were ultimately diagnosed as TM. Although Dr. Gershwin's opinions about the innate immune system and the interplay between it and the adaptive immune system were persuasive and sound, to the extent that he opined that the innate immune response alone could cause TM, the undersigned finds those opinions to be questionable. In short, the undersigned finds that some of Dr. Gershwin's opinions were inapposite to established medical literature and prior Vaccine Program cases that have acknowledged molecular mimicry and the adaptive immune system as the applicable causal theory implicated in vaccine associated TM.

Dr. Forsthuber persuasively explained why the innate immune response does not fit in the context of TM. He effectively explained that the blood-brain barrier protects against large proteins, including IgM antibodies, which form the basis of the immune response suggested by Dr. Gershwin. Moreover, Dr. Forsthuber explained that IgM antibodies are generally "directed against lipids" and the "[p]ertussis toxin is not lipid." Tr. 300.

Moreover, literature cited by Dr. Gershwin does not support his position that the Tdap vaccine induces increased levels of cytokines in the blood. Lim et al. and Kleiner et al. found no significant changes in the level of cytokines. Grigg et al. discussed pro-inflammatory T cells

(ILC3s) in the CNS and their role in "autoimmune neuroinflammation" relative to the pathogenesis of multiple sclerosis type illnesses. Pet. Ex. 48 at 1. Dr. Forsthuber effectively explained that the adaptive immune response is required for the recruitment of ILC3 cells to the brain, which then induce neuroinflammation.

Further, the Hervé et al. article cited by Dr. Gershwin does not explain how a vaccination can, through an IgM response, cause inflammation within the spinal cord in the span of approximately 24 hours to cause TM.

For these reasons, the undersigned finds that Dr. Gershwin's theory based on an innate immune response is not sound or reliable to explain how the Tdap vaccine causes TM.

Lastly, Petitioner presented the opinions of Dr. Conomy and Dr. Steinman based on molecular mimicry, along with supportive literature.

Dr. Steinman provided an example of homology using his three-step process employing a BLAST search and the IEDB database. In response, Dr. Forsthuber methodically and effectively discredited Dr. Steinman's example, showing why it was unlikely to illicit an autoimmune response. Although Dr. Steinman's example was effectively discredited, this did not invalidate Petitioner's experts' opinions establishing molecular mimicry as a sound and reliable theory explaining how the Tdap vaccination can cause TM. There are several reasons that the undersigned finds molecular mimicry is a sound and reliable mechanism here.

First, the medical literature filed by Petitioner establishes that molecular mimicry is a well-known immune response in immunology that has been identified in medical literature as a mechanistic theory for how infectious agents and vaccines can cause autoimmune disorders like TM. Agmon-Levin et al. described the mechanism of molecular mimicry as the "most common" or postulated mechanism by which infectious agents or vaccinations can cause autoimmune diseases like TM. Pet. Ex. 8.8 at 4. The authors reviewed 37 cases of post-vaccination TM, including post-DTP and post-DT vaccination, and found 30 of the 37 cases developed symptoms of TM within two months after vaccination.

In addition, Petitioner cited case reports of TM associated with DTaP vaccination. Riel-Romero described a case of a patient who developed TM after DTaP vaccination. The authors hypothesized that their patient's TM was caused by vaccination and found an immune-mediated process to be at play, specifically noting molecular mimicry as a postulated mechanism.

Generally, case reports and literature reviews citing cases are insufficient to prove causation. However, in the context of rare conditions like TM, they provide some evidence of causation. And here, where the medical literature reported TM cases associated with vaccines containing tetanus and/or diphtheria components, this evidence weighs in favor of causation.

Secondly, Petitioner need not make a specific type of evidentiary showing or require identification of homology to prove that molecular mimicry is a sound and reliable theory by preponderant evidence. Given the state of current scientific knowledge, there is no way that a petitioner could satisfy such a requirement. Further, requiring proof of specific homology or

proof of identical protein sequences between the Tdap vaccine and the CNS to prove causation would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

Regarding Dr. Steinman's testimony about sequences of similar amino acids, the undersigned finds that he was providing an example to illustrate homology as a way to explain the science using readily available resources. Dr. Steinman explained that he could not perform research on Petitioner. He also explained the limitations of the process that he used. It would be an extreme response to reject the mechanistic theory of molecular mimicry because Dr. Steinman offered an example that was disproved. The undersigned is not willing to throw out the proverbial baby with the bathwater, or disregard applicable medical literature, or ignore her knowledge and experience, when molecular mimicry has been repeatedly shown by preponderant evidence to be a sound and reliable theory in the context of vaccine causation.

Lastly, molecular mimicry has been accepted as a sound and reliable theory for many demyelinating conditions, including TM, in the Vaccine Program. See, e.g., Palattao v. Sec'y of Health & Hum. Servs., No. 13-591V, 2019 WL 989380, at *35-37 (Fed. Cl. Spec. Mstr. Feb. 4, 2019) (noting "many of the existing Program decisions in which TM has been found to be caused by a vaccine rely on a mechanism [of] []molecular mimicry"); Raymo v. Sec'y of Health & Hum. Servs., No. 11-0654V, 2014 WL 1092274, at *21 (Fed. Cl. Spec. Mstr. Feb. 24, 2014) (former Chief Special Master Denise Vowell concluding that molecular mimicry explained how the tetanus vaccine can cause TM); Roberts v. Sec'y of Health & Hum. Servs., No. 09-427V, 2013 WL 5314698, at *6-7 (Fed. Cl. Spec. Mstr. Aug. 29, 2013) (finding the Petitioner entitled to compensation in a Tdap/TM case with the theory of molecular mimicry); see also Bowes v. Sec'y of Health & Hum. Servs., No. 01-481V, 2006 WL 2849816 (Fed. Cl. Spec. Mstr. Sept. 8, 2006). Compare Palattao, 2019 WL 989380, at *35-37 (Chief Special Master Corcoran denying entitlement in a TM case where the facts did not support application of molecular mimicry), with I.J. v. Sec'y of Health & Hum. Servs., No. 16-864V, 2022 WL 277555, at *4-7 (Fed. Cl. Spec. Mstr. Jan. 4, 2022) (Chief Special Master Corcoran finding Petitioner entitled to compensation on remand in a Tdap/TM case that relied upon the theory of molecular mimicry).

While the above cases are not binding here, the undersigned agrees with the reasoning of other special masters who have found molecular mimicry to be a sound and reliable mechanism to explain how the Tdap vaccine can cause TM. Moreover, the undersigned recently held that the Tdap vaccine can cause TM via molecular mimicry. See Introini v. Sec'y of Health & Hum. Servs., No. 20-176V, 2022 WL 16915818 (Fed. Cl. Spec. Mstr. Oct. 19, 2022).

For all of these reasons, the undersigned finds the Petitioner has established by preponderant evidence that molecular mimicry is a sound and reliable mechanism by which the Tdap vaccination can cause TM, therefore satisfying Althen Prong One.

B. Althen Prong Two

Under Althen Prong Two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for

the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Regarding Althen Prong two, the undersigned finds there is preponderant evidence in the record to support a logical sequence of cause-and-effect showing Petitioner's Tdap vaccine to be the cause of his TM because his medical records show evidence that he sustained an autoimmune illness consistent with the causal theory of molecular mimicry, his physicians supported vaccine causation, and there is no evidence of any alternative cause.

Petitioner's experts set out convincing reasons why the facts of the case are consistent with an autoimmune condition caused by molecular mimicry. The CSF showed the presence of inflammatory cells, increased protein, and oligoclonal bands indicating an IgG immune response. Further, the MRI showed enhancement and slight expansion of the spinal cord at T-6.

Additionally, in determining whether Petitioner has put forth preponderant evidence of Althen Prong Two, the undersigned generally takes into consideration the opinions of the treating physicians. Treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views are carefully considered and evaluated. § 13(b)(1); Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 746 n.67 (2009). "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

Here, Petitioner's treating physicians related Petitioner's TM to his Tdap vaccine. For example, Dr. Chay opined that within "a reasonable degree of medical and scientific certainty . . . the [Tdap] shot . . . was the etiology of [TM]." Pet. Ex. 5 at 2. And Dr. Gillon wrote that a "reaction to the [Tdap] shot could be a potential cause of his [TM]." Pet. Ex. 2 at 9; see also id. at 4 (Dr. Khoury questioning whether the Tdap shot had to do with Petitioner's TM).

Lastly, there is no evidence of an alternative cause. Petitioner did not have any signs or symptoms of an infection prior to onset of his TM. Numerous diagnostic studies were performed on the CSF, including Lyme, CMV, HSV, and others, and the results were normal, and did not reveal any infectious or other cause for Petitioner's TM.

Accordingly, the undersigned finds that Petitioner has satisfied his burden under Althen Prong Two.

C. Althen Prong Three

Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. The Petitioner must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see also Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that [P]etitioner must posit a medical theory causally connecting the vaccine and injury").

Petitioner's experts place onset of his TM at 48 to 72 hours. Dr. Conomy opined that onset occurred in a "couple to a few days." Pet. Ex. 8 at 6. Dr. Steinman found onset to be 48 to 72 hours. In contrast, Respondent's experts place onset at 24 to 48 hours. The undersigned agrees with Petitioner's experts' opinions on this issue, and finds onset was May 22 and/or May 23, approximately 48 to 72 hours after vaccination, for the following reasons.

The literature filed herein describes the presentation of TM; it is characterized by symptoms and signs of neurologic dysfunction, including motor dysfunction, sensory dysfunction, and autonomic dysfunction attributable to the spinal cord. Motor dysfunction is often described as weakness. Autonomic dysfunction is described as bladder impairment. Sensory dysfunction is described as "numbness, paresthesias, or band-like dysesthesias." Pet. Ex. 11.5 at 1. The inclusion criteria developed by the TM Consortium Working Group identifies "[d]evelopment of sensory, motor, or autonomic dysfunction attributable to the spinal cord" as criteria for diagnosis. Id. at 2 tbl.1. In summary, the literature and the TM Consortium Working Group use the triad of motor dysfunction, sensory dysfunction, and autonomic (bladder impairment) to describe the symptoms which herald TM. Thus, the undersigned uses this framework to determine onset.

The experts disagree as to the significance of Petitioner's "foot stiffness," which began late at night on May 21, just over 24 hours after vaccination. Dr. Steinman opined that foot stiffness is not a typical manifestation of TM. To place onset at the time of this symptom, one must interpret the word "stiffness" as meaning something more. Respondent's experts interpret it to mean "numbness" or "weakness." See Tr. 162-63, 178, 182. Petitioner's experts disagree and express reluctance about using stiffness as a symptom because they argue it is not typical. The undersigned agrees with Petitioner's experts. To use it as a benchmark of onset requires interpretation. Thus, the undersigned declines to use it to mark the initial manifestation of Petitioner's TM.

In addition to the quandary about the significance of "foot stiffness," onset is difficult because the medical histories provide a summary of events as opposed to a day-by-day chronology. The histories, while informative for the purpose of diagnosis, do not provide a time-line to allow a reasonable determination of exactly when Petitioner first experienced motor, sensory, and autonomic dysfunction. In other words, the events of several days are condensed into one or two sentences making it difficult to discern what happened when. For example, Dr. Rodgers documented that "[o]ver the last week, [Petitioner] has had increasing weakness in his lower extremities to the point that he was unable to walk." Pet. Ex. 2 at 11. And Ms. Kerrigan notated Petitioner's "[bilateral] [lower extremity] weakness and urinary retention worsening [for] 3 d[ays], unable to stand or void." Id. at 21. Other histories summarized a progressive process but it is difficult to determine precise onset from them.

The Vaccine Act does not define the meaning of the phrase, "the first symptom or manifestation of the onset." § (c)(1)(C)(i). The Vaccine Injury Table does not provide guidance either. 42 C.F.R. § 100.3(a) (noting "time period in which the first symptom or manifestation of onset . . . after vaccine administration"). However, there is some guidance from case law. "'[T]he first symptom or manifestation of onset' . . . is the first event objectively recognizable as a sign of a vaccine injury by the medical profession at large." Markovich v. Sec'y of Health & Hum. Servs., 477 F.3d 1353, 1360 (Fed. Cir. 2007). Further, the Federal Circuit held "the statute of limitations of the Vaccine Act begins to run on the calendar date of the occurrence of the first medically recognized symptom or manifestation of onset of the injury." Cloer v. Sec'y of Health & Hum. Servs., 654 F.3d 1322, 1324-25 (Fed. Cir. 2011) (en banc). Following this guidance, it is appropriate to place onset at the time of a "medically recognized symptom."

The undersigned finds that the medical literature and Dr. Steinman offer the most reasonable and persuasive benchmarks for onset consistent with medically recognized symptoms of TM based on when Petitioner began having difficulty walking (motor dysfunction) and bladder dysfunction.[89] In several of the medical histories, the health care providers state that Petitioner had difficulty walking and inability to void on May 23, 2014. Unlike "foot stiffness," using these complaints is consistent with the use of "medically recognized symptoms" for onset. The following records describe Petitioner's difficulty walking and/or inability to void.

[89] Dr. Steinman also relied on the onset of Petitioner's back pain as a marker for onset. The undersigned does not use this marker. While the medical literature does refer to pain, it is not part of the initial triad which was consistently used in the literature to describe the clinical presentation of TM.

Petitioner received the Tdap vaccine on May 20, 2014 between 5:00 PM and 6:00 PM. He presented to the ED on the morning of May 24, 2014. An initial history documented on May 24 at 9:33 AM states that Petitioner began having "difficulty walking yesterday." Pet. Ex. 2 at 28. Based on this note, the onset of Petitioner's "difficulty walking" began on May 23. On May 25, Dr. Khoury noted that Petitioner received his Tdap vaccination on Tuesday (May 20), and that two or three days ago (May 22 or 23), Petitioner was unable to void his urine. Id. at 3. Also on May 25, Dr. Tepper documented that two days ago (May 23) Petitioner experienced difficulty moving his legs and was unable to walk. Id. at 5.

In summary, contemporaneous records by health care providers place the onset of Petitioner's difficulty walking and bladder dysfunction on May 22 and/or May 23, approximately 48 to 72 hours after vaccination.

Having determined onset to be 48 to 72 hours, the next question is whether there is "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. Dr. Conomy opined that cases of TM due to Tdap vaccine via molecular mimicry have occurred within a couple to a few days, which the undersigned interprets to be two to three days. See Jewell v. Sec'y of Health & Hum. Servs., No. 16-0670V, 2017 WL 7259139, at *3 (Fed. Cl. Spec. Mstr. Aug. 4, 2017) (finding "a few days" after vaccination to be within 72 hours); Taylor v. Sec'y of Health & Hum. Servs., No. 16-1403V, 2020 WL 6706078, at *16 (Fed. Cl. Spec. Mstr. Oct. 20, 2020) (finding "few" to mean two or three days). Similarly, Dr. Steinman opines that an onset of 48 to 72 hours is an appropriate temporal interval for his proposed mechanism of molecular mimicry. Moreover, an onset of three days for molecular mimicry is supported by the medical literature as an appropriate temporal association. In Agmon-Levin et al., post-vaccination TM occurred in a range of two days to three months. Pet. Ex. 8.8 at 3 tbl.1. And an early onset of two, three, and four days was reported in three cases.

Additionally, this timing is within the two- to 42-day risk interval used in Baxter et al. Although the authors found "no statistically significant increased risk" of TM post-vaccination within the two- to 42-day risk interval, the authors did find cases of TM that occurred within and outside of this interval. Resp. Ex. A, Tab 9 at 3. Even Respondent's expert, Dr. Gelfand, specifically noted that Baxter et al. drew a line for onset at two days or 48 hours. Tr. 192.

While two to three days is an early onset, it is within the onset dates identified in Agmon-Levin et al. and the two-day risk window in Baxter et al. See Paluck v. Sec'y of Health & Hum. Servs., 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) (finding the "special master [] erred in setting a hard and fast deadline . . . between vaccination and [] onset"). Therefore, it reasonable and appropriate to find that the onset of Petitioner's TM is within the appropriate timeframe given the mechanism of molecular mimicry.

Thus, the undersigned finds the temporal association is appropriate given the mechanism of injury and Petitioner has satisfied the third Althen prong.

D. Alternative Causation

Because the undersigned concludes that Petitioner has established a prima facie case, Petitioner is entitled to compensation unless Respondent can put forth preponderant evidence "that [Petitioner's] injury was in fact caused by factors unrelated to the vaccine." Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). Here, the undersigned finds that Respondent failed to show that Petitioner's TM was caused by a source other than vaccination. Thus, Respondent did not prove by a preponderance of evidence that Petitioner's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

VI. CONCLUSION

For the reasons discussed above, the undersigned finds that Petitioner has established, by preponderant evidence, that his Tdap vaccine caused his TM. Therefore, Petitioner is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master