In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: November 4, 2019

GEORGE SWAISS,	*	PUBLISHED
Petitioner,	*	No. 15-286V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus-Diphtheria-Acellular Pertussis ("Tdap"); Small Fiber Neuropathy; Guillain-Barré syndrome ("GBS"); Molecular Mimicry.
Respondent.	*	

Ronald C. Homer & Joseph M. Pepper, Conway Homer, P.C., Boston, MA, for petitioner.[1]
Adriana R. Teitel & Lynn E. Ricciardella, U.S. Department of Justice, Washington, DC, for respondent.[2]

RULING ON ENTITLEMENT[3]

On March 19, 2015, George Swaiss ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program.[4] Petition (ECF No. 1). Petitioner alleges that as a result of receiving a tetanus-diphtheria-acellular pertussis ("Tdap") vaccination on June 1, 2012, he has suffered a small fiber neuropathy which constitutes a variant of Guillain-Barré

[1] Mr. Homer is petitioner's attorney of record, while Mr. Pepper filed petitioner's pre- and post-hearing briefs and appeared at the entitlement hearing.

[2] Ms. Teitel is respondent's current attorney of record. Respondent's previous attorney of record Lynn E. Ricciardella filed respondent's pre- and post-hearing briefs and appeared at the entitlement hearing.

[3] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this opinion contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the opinion will be available to anyone with access to the Internet.** Before the opinion is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). An objecting party must provide the court with a proposed redacted version of the opinion. *Id.* **If neither party files a motion for redaction within 14 days, the opinion will be posted on the court's website without any changes.** *Id.*

[4] 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-1 to 34 (2012) ("Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

syndrome ("GBS"). *Id.* at Preamble; Petitioner's ("Pet.") Post-Hearing Brief (ECF No. 88) at 1. Based on a full review of all of the evidence and testimony presented, I find that petitioner is entitled to compensation.[5]

I. Procedural History

On March 19, 2015, petitioner filed the petition which alleges that he suffered a "neurological injury" as a result of the Tdap vaccination received on June 1, 2012. Petition at Preamble. During an initial status conference in April 2015, I stated that petitioner should clarify the nature of his injury and that his symptoms were suggestive of a small fiber neuropathy. Initial Order (ECF No. 8); *see also* Scheduling Order filed on October 25, 2016 (ECF No. 42). In August 2015, petitioner sent a demand to respondent. Pet. Status Report (ECF No. 11). In September 2015, respondent advised that the case was appropriate for settlement discussions. Respondent's ("Resp.") Status Report (ECF No. 12). In spring 2016, the parties communicated that they could not resolve their differing assessments of petitioner's diagnosis, entitlement, and damages. Thus, they proceeded on a litigation track. Status Report (ECF No. 26); Scheduling Order (ECF No. 27).

On July 26, 2016, petitioner filed an expert report from Dr. Nizar Souayah, who opined that as a result of the Tdap vaccination, petitioner developed a GBS small fiber variant. Pet. Ex. 14 (ECF No. 33).[6] On October 14, 2016, respondent filed a responsive expert report from Dr. Peter Donofrio, Resp. Ex. A (ECF No. 40)[7], and a report pursuant to Vaccine Rule 4(c) recommending against compensation. Respondent's Report ("Resp. Rep't") (ECF No. 39).

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[5] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

[6] Dr. Nizar Souayah gained primary care and family practice experience from 1987 to 1990 at the Medical School of Tunis in Tunisia, from which he obtained his medical degree in 1990. Pet. 15 at 1. He was a resident in internal medicine and vascular disease at a teaching hospital in Strasbourg, France, from 1992 to 1997. *Id.* at 1. He held an internship followed by a residency in internal medicine at the University of Pennsylvania Health System in Philadelphia, Pennsylvania from 1997 to 1999. *Id.* at 1. Afterwards, at Temple University Hospital (also in Philadelphia), he completed an internship followed by a residency in neurology from 1999 to 2000, then served as chief resident from 2002 to 2002. *Id.* From 2002 to 2003, he held a fellowship in electromyography (EMG) and neuromuscular disease at Harvard Medical School in Boston, Massachusetts. *Id.* From 2003 to 2004, he held a fellowship in neuroscience, focusing on neuroinflammation in neurodegenerative disorders at Drexel Medical School in Philadelphia, Pennsylvania. *Id.* In 2004, Dr. Souayah joined Rutgers, the University of New Jersey Medical School, where he has become the director of the Peripheral Neuropathy Center and EMG Laboratory. *Id.*; Tr. 5. He continues to teach medical students and neurology residents. Tr. 10. He is licensed to practice medicine in the state of New Jersey and is board-certified in neurology, neuromuscular medicine, and electrodiagnostic medicine. Tr. 6. He has treated and continues to treat patients with GBS and small fiber neuropathy. Tr. 11. He also serves as the Executive Editor of the Journal of Vaccines and Vaccination and actively contributes research to the field. Tr. 8. Petitioner proffered and I accepted Dr. Souayah as an expert in the field of neurology. Tr. 11.

[7] Dr. Peter Donofrio obtained a bachelor's degree in pre-professional science from the University of Notre Dame in 1972 and a medical degree from the Ohio State University School of Medicine in 1975. Resp. Ex. B at 1. He completed a residency in internal medicine at Good Samaritan Hospital in Cincinnati, Ohio from 1975 – 1978. *Id.* He then went to the University of Michigan, where he completed a residency in neurology from 1978 – 1981, a fellowship in neuromuscular disease from 1981 – 1982, and served on the medical school faculty from 1981 – 1985. *Id.* From 1986 to 2006, he served on the faculty at Wake Forest University Medical School. *Id.* In 2006, Dr.

On October 24, 2016, petitioner filed updated medical records including QSART testing and a skin biopsy showing a small fiber neuropathy. Pets. Exs 16-18 (ECF No. 41). On October 25, 2016, I held a status conference pursuant to Vaccine Rule 5. I stated that the QSART testing and skin biopsy confirmed a small fiber neuropathy and the symptoms seemed to arise within a reasonable time after the Tdap vaccine. I placed the case on dual tracks towards informal resolution and towards an entitlement hearing. Scheduling Order (ECF No. 42). The parties engaged in further settlement discussions for nearly a year but then advised that settlement was not possible. Resp. Status Report (ECF No. 61).

The case was scheduled for an entitlement hearing. Hearing Order filed January 3, 2017 (ECF No. 50); Scheduling Order filed December 14, 2017 (ECF No. 68); Hearing Order filed December 27, 2017 (ECF No. 72). The parties filed pre-hearing briefs. Pet. Pre-Hearing Brief filed November 22, 2017 (ECF No. 67); Resp. Pre-Hearing Response filed January 5, 2018 (ECF No. 76).

On February 12, 2018, an entitlement hearing took place in Washington, DC. The witnesses were Dr. Souayah and Dr. Donofrio. *See* Post-Hearing Order filed February 14, 2018 (ECF No. 83) Transcript ("Tr.") filed March 5, 2018 (ECF No. 85). The parties filed post-hearing briefs. Pet. Post-Hearing Brief filed May 14, 2018 (ECF No. 88); Resp. Post-Hearing Response filed August 1, 2018 (ECF No. 92). Petitioner did not file a reply. The matter is now ripe for adjudication.

II. Legal Standard[8]

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-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 & Human Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

Donofrio was hired by the Vanderbilt University School of Medicine, where he currently serves as a Professor of Neurology, the Vice President of Clinical Affairs, and the director of the Muscular Dystrophy Association ("MDA") Clinic, the Amyotrophic Lateral Sclerosis ("ALS") Clinic, and the Neuromuscular Program. *Id.* He is licensed to practice medicine in the state of Tennessee and is board-certified in internal medicine, neurology, neuromuscular medicine, and EMG. *Id.* Dr. Donofrio continues to teach medical students, residents, and fellows. Tr. 83. He has and continues to diagnose and treat patients, including those with GBS and small fiber neuropathy. *Id.* at 84-85. He is a member of several medical societies and has edited and published in reputable medical publications. *See also* Resp. Ex. B. Dr. Donofrio commented that he had a "very similar focus to Dr. Souayah," on "neuromuscular disorders, many very similar to his." Tr. 82. Respondent proffered and I accepted Dr. Donofrio as an expert in neurology, electrodiagnostic medicine, and neuromuscular medicine. *Id.* at 87.

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

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. There are two avenues to compensation. The first requires the petitioner to demonstrate a Table injury but that is not alleged in the present case. The second avenue requires the petitioner to prove that a vaccine listed on the Vaccine Table was the cause-in-fact of the injury.

To prove causation-in-fact, the petitioner must "show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination and injury; 2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and 3) a showing of proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.,* 418 F. 3d 1274, 1278 (Fed. Cir. 2005). There must be preponderant evidence for each *Althen* prong. *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 132 (2011), *aff. per curiam,* 463 Fed. Appx. 932 (Fed. Cir. 2012).

The preponderance of the evidence standard requires demonstrating that it is "more likely than not" that the vaccine caused the injury. *Moberly v. Sec'y of Health & Human Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner must demonstrate 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 v. Sec'y of Health & Human Servs.*, 135 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Pafford v. Sec'y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation is determined on a case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon "circumstantial evidence" which is consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen,* 418 F. 3d at 1280.

A petitioner often presents expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.,* 219 F.3d 1357, 1361 (Fed. Cir. 2000). Expert testimony in the Vaccine Program is usually evaluated according to the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo,* 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.,* 195 F.3d 1302, 1316 (Fed. Cir. 1999). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly* at 1324. The *Daubert* factors are used in *weighing* the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.,* 94 Fed. Cl. 53, 66-67 (2010). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.,* 219 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe,* 219 F.3d 1357 at 1362).

Once a petitioner has proven causation by preponderant evidence, the burden shifts to respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine. *Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally

responsible' for the injury. If the evidence or alternative cause is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen,* 35 F.3d at 551.

III. Summary of Relevant Facts

A. Petitioner's History Before June 1, 2012 Tdap Vaccination

Petitioner George Swaiss was born on May 12, 1966. Ex. 2 at 1. In 2012, he was married and raising three young children. Pet. Ex. 3 at 1. He had been working as a mechanical engineer for NASA for over twenty (20) years. *Id.* He had owned and maintained four rental apartments since 1998. *Id.* at 5. He had been riding motorcycles as a hobby and a source of stress relief since 1986. *Id.*

Petitioner received primary and specialty medical care through the Kaiser Permanente managed care consortium. He was noted to have hypertension[9] in July 2005, migraine[10] in March 2008, and neck pain in July 2008. Pet. Ex. 2 at 1. In November 2008, it was noted that after taking ciprofloxacin,[11] he had developed "muscle ache," also described as "muscle and neuropathic pain[12] in hips, legs, and feet." *Id.* In 2009, he went to physical therapy for left-sided neck and upper back "myofascial pain"[13]. *Id.* at 109. There are no records of muscle, neuropathic, and/or myofascial pain from 2009 to 2012. Both parties' experts reviewed the available medical records, but they did not opine about the prior history. Respondent's expert Dr. Donofrio was asked whether petitioner "was experiencing neuropathic pain prior to his Tdap vaccine." Dr. Donofrio responded: "Not that I could find." Tr. 132.

On June 1, 2012, petitioner presented to Dr. Eric Messner at Kaiser Permanente Santa Clara Medical Center for a routine physical examination. His blood pressure was 131/81. He reported symptoms of carpal tunnel syndrome and restless leg syndrome. However, the physical examination was unremarkable. On neurological exam, petitioner was "alert, oriented, normal speech, no abnormal sensation or abnormal reflexes. No focal neurological findings." Pet. Ex. 2 at 15-19. Petitioner also reported some difficulty with focus and concentration; he saw parallels

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[9] Hypertension is "high arterial blood pressure." *Dorland's Illustrated Medical Dictionary* 32nd Ed. (2012) (hereinafter "*Dorland's*") at 896.

[10] Migraine is "an often familial symptom complex of periodic attacks of vascular headache, usually temporal and unilateral in onset, commonly associated with irritability, nausea, vomiting, constipation or diarrhea, and often photophobia." *Dorland's at* 1166.

[11] Ciprofloxacin (often referred to by the trademarked brand name cipro) is used to treat a wide variety of bacterial infections. It is administered orally, intravenously, and topically. *Dorland's* at 362-63.

[12] Neuropathic pain "results from direct stimulation of nervous tissue of the peripheral or central nervous system… generally felt to as burning or tingling and often occurring in an area of sensory loss." *Dorland's* at 1363.

[13] Myofascial pain is "attributed to trigger points in muscles and their fascia, with more specific points of origin than with fibromyalgia." *Dorland's* at 1363.

to the experience of his adult brother, who had recently been diagnosed with ADD.[14] Dr. Messner sent a consult request to psychiatry. During this appointment, petitioner received the Tdap vaccination at issue, as an intramuscular injection in his left arm. Pet. Ex. 2 at 15-19.

B. Petitioner's History After June 1, 2012 Tdap Vaccination

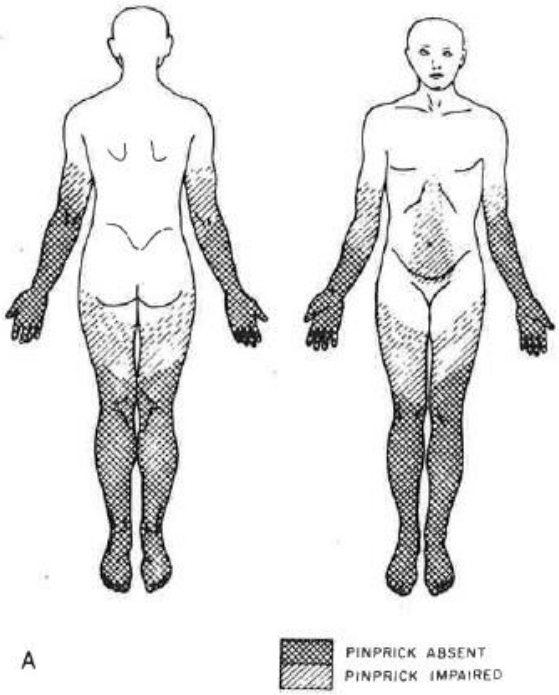
On Friday, June 8, 2012, petitioner emailed Dr. Messner reporting severe pain in his upper left shoulder muscle, pain and weakness in his left forearm and palm, a bitter taste in his mouth, and flu symptoms. Pet. Ex. 2 at 48. Dr. Messner noted that petitioner had received a Td vaccine in 2001 with no problems. He questioned whether petitioner was having a reaction to the acellular pertussis component of the recent Tdap vaccine. Dr. Messner directed petitioner to undergo lab work, which he did the following day, Saturday, June 9, 2012. *Id.* at 52-54.

On Monday, June 11, 2012, Dr. Messner saw petitioner for a follow-up appointment. The labwork was normal. Petitioner was concerned about a reaction to the Tdap vaccine and was concerned that he had GBS. His left arm pain had abated, but he continued to have the bitter taste. He had also developed facial numbness and tightness, numbness on the bottom of his feet, and pain in his legs and groin. He had difficulty walking because his leg muscles were fatiguing more quickly and he needed to stop more frequently to rest. Physical examination confirmed sensations of numbness on the face, forearms, palms, and soles of the feet. Reflexes and muscle strength were normal. Dr. Messner's assessment was "Dysesthesias[15] following Tdap vaccination – etiology unclear." He also wrote: "? Variant of guillain barre (although ssx not strictly ascending). ? More demyelinating process ?" Dr. Messner referred to a neurologist, Dr. Jai Hee Cho, also within the Kaiser Permanente network. Pet. Ex. 2 at 57-59.

That same day, June 11, 2012, Dr. Cho saw petitioner for an initial consult. She obtained a more detailed history. Petitioner first experienced pain in the left deltoid. Then on June 8, 2012, he developed pain and weakness in the left forearm and hand. He had trouble gripping the clutch on his motorcycle. On June 9, 2012, he developed pain in his face, feet, and calves; full body aches; difficulty standing; and fatigue. His blood pressure was elevated at 175/94. On June 10, 2012, petitioner still had full body aches and fatigue. He also developed tingling in his hands. Over the course of the weekend, these symptoms made it difficult for petitioner to attend several graduation parties and church service. On neurological exam, Dr. Cho found that petitioner had reduced pin-prick sensation on the right side of the face, mid-forearms, and mid-thighs. He had normal reflexes and "give-way" strength. At Dr. Cho's direction, petitioner was able to complete "10 sit/ stands without using hands" and "get from floor without using hands." However, both of those exercises "caused pain." Pet. Ex. 2 at 62. Dr. Cho "agree[d] that the clinical picture [was] most consistent with a sequelae to dTap." *Id.* Petitioner's sensory loss was in a "stocking-and-glove" pattern as seen below:

[14] Attention deficit disorder ("ADD") is a mental disorder characterized by inattention, hyperactivity and impulsivity, or by both types of behavior. *Dorland's* at 547-58.

[15] Dysesthesia is "distortion of any sense, especially that of touch." *Dorland's* at 577.



Dyck and Thomas, *Peripheral Neuropathy* (4th ed. 2005) at 1139, Fig. 45-2. Dr. Cho recorded that this was consistent with peripheral nervous system involvement. Pet. Ex. 2 at 62. However, the presence of brisk ankle jerks and knee jerks "went against a diagnosis of GBS." Dr. Cho's differential diagnosis included GBS and ADEM. Dr. Cho estimated that petitioner's symptoms had been present for at least four days and "typically symptoms plateau around day 7 – 10." *Id.* Dr. Cho reasoned that petitioner's reflexes were brisk and the symptoms were mostly sensory, so they could do a "speedy workup as an outpatient." She scheduled MRIs of the brain and cervical spine, a lumbar puncture, and a multiple sclerosis panel. She prescribed clonazepam[16] for symptom relief that evening. She noted that gabapentin[17] also worked well for burning pain, though she did not prescribe it at that time. *Id.* at 63-64.

The next day, June 12, 2012, Dr. Cho saw petitioner again. The brain and cervical spine MRIs, lumbar puncture, and multiple sclerosis panel were all normal. Pet. Ex. 2 at 67-76, 79-91. Petitioner felt about the same to slightly better. He believed that his symptoms were plateauing. Dr. Cho suspected that petitioner had a "peripheral nervous system problem, variant of GBS."

[16] Clonazepam is a benzodiazepine used to prevent both seizures and panic attacks. *Dorland's* at 373. It "works by calming your brain and nerves." WebMD, *Klonopin (Generic Name: Clonazepam)*, available at https://www.webmd.com/drugs/2/drug-920-6006/klonopin-oral/clonazepam-oral/details (last accessed October 25, 2019).

[17] Gabapentin is an anti-convulsant. *Dorland's* at 753. It "affects chemicals and nerves in the body which are involved in the cause of seizures and some types of pain" and is used "to treat neuropathic pain (nerve pain"). Drugs.com, *Gabapentin*, available at https://www.drugs.com/gabapentin.html (last accessed October 25, 2019).

They "talked about IVIg[18] but after careful discussion of pros/ cons, decided not to proceed at this time." Petitioner would continue to take clonazepam and add gabapentin. *Id.* at 76-77.

On June 18, 2012, petitioner emailed Dr. Cho that most of his pain was gone, but he was having mental fog and a slight lack of balance. Dr. Cho responded that he was still recovering and he should give it a few more days. Pet. Ex. 2 at 99. On June 20, 2012, Dr. Messner recorded that petitioner was improving but still had some pain, anxiety, and issues with focus and concentration. Dr. Messner recommended increasing gabapentin. Pet. Ex. 2 at 101-02.

On June 25, 2012, Dr. Messner emailed petitioner. Dr. Messner and Dr. Cho agreed that petitioner "had a very idiosyncratic reaction to the Tdap vaccine and [his] body will right itself over the next 3-6 weeks." He should continue taking gapabentin and clonazepam. Dr. Cho "didn't recommend any prednisone or any medication at this juncture", because those had side effects and petitioner did not have "progressive muscle weakness." Pet. Ex. 2 at 104-05.

On June 29, 2012, Dr. Cho recorded that petitioner was stable overall. He was going to work regularly but was experiencing pain, weakness, blurred and double vision, and poor balance. He also reported cognitive issues, which Dr. Cho believed might be due to clonazepam. Petitioner would decrease clonazepam and increase gabapentin. Dr. Cho recommended an EMG/NCV to evaluate for peripheral nervous system involvement as well as physical therapy and seeing an eye doctor. Dr. Cho recorded that petitioner's course had been stable and it was "medically safe for him to travel to Jordan (month of Aug)". Pet. Ex. 2 at 108-10.

In an affidavit submitted alongside the petition, petitioner explained that in May 2012, his three young children traveled to Jordan to visit his parents, who lived in the country. In August 2012, petitioner joined his family in Jordan. His pain "continued throughout this trip." "At one point, [he] tried to carry my kids into the house from the car while they were sleeping and was unable to do it so [he] had to wake them up." Pet. Ex. 3 at 3. It is unclear exactly when petitioner returned to the United States.

On September 19, 2012, Dr. Messner saw petitioner again and recorded that he had GBS with "ongoing flares of pains throughout his body." Gabapentin helped but did not fully address these pains. Dr. Messner added duloxetine hydrochloride.[19] Pet. Ex. 2 at 118-20. Also on September 19, 2012, petitioner underwent an EMG/NCV of the bilateral lower extremities which did not show "evidence of large fiber sensorimotor neuropathy or myopathy." Pet. Ex. 2 at 121-24. On September 20, 2012, Dr. Cho emailed petitioner that the EMG/NCS was "normal" but "it does not check for small nerve fiber neuropathy." *Id.* at 125.

[18] As discussed further below, intravenous immunoglobulin therapy ("IVIg") is often used in the treatment of GBS.

[19] Duloxetine hydrochloride (referred to in the medical records by the trademark name Cymbalta) is "a serotonin-norepinephrine reuptake inhibitor, used for the treatment of major depressive disorder and the relief of pain In diabetic neuropathy." *Dorland's* at 572; *see also id.* at 457.

On January 24, 2013, Dr. Messner recorded that petitioner continued to have muscle achiness and fatigue, particularly with exertion and as the day went on. Gabapentin helped but caused sedation, so he could not take it during the day. Dr. Messner's assessment was neuropathic pain. Petitioner would continue gabapentin, add piroxicam[20] during the day, and follow up with Dr. Cho. Dr. Messner noted that petitioner was seeing a psychiatrist for depression. Pet. Ex. 2 at 130-32.

On March 15, 2013, Dr. Cho recorded that petitioner's symptoms began after the June 1, 2012 Tdap vaccination and stabilized after "a few weeks". However, he continued to have pain at 2/10 upon waking up and at 10/10 by the end of the work day. His job was moderately physical (walking 50% of the 8-hour day). On weekends, his pain was at 4/10. Gabapentin helped. Dr. Cho disagreed with petitioner's suggestion of CIDP and his request for a nerve muscle biopsy. Instead, Dr. Cho recommended a follow-up EMG/NCS, anti-anxiety medications, and pain management. He also referred petitioner for a second opinion to Dr. Manjari Patel, another neurologist within the Kaiser Permanente network. Pet. Ex. 2 at 144-45.

On March 25, 2013, Dr. Patel had his first and only appointment with petitioner. Dr. Patel reviewed the previous Kaiser Permanente chart, including one episode in 2008 when petitioner took ciprofloxacin and subsequently developed pain in the groin and legs, and several medical appointments in 2008 – 2009 for "left neck/ upper back pain radiating down LUE" which was eventually diagnosed as "myofascial pain". Pet. Ex. 2 at 148. Dr. Patel recorded that there was a temporal association between the Tdap vaccine and the subsequent onset of symptoms. The neurologic exam was "largely intact with the main findings being sensory and not always following neuroanatomic patterns (such as facial numbness)." *Id.* at 150. "There [we]re no objective findings to suggest injury to the nervous system." *Id.* Dr. Patel's impression was myofascial pain. Petitioner was convinced that he had experienced an autoimmune response to the Tdap vaccine and asked for any medication for this. Dr. Patel advised that there was not a clear-cut clinical picture or neurologic abnormality indicating that "steroids or immunosuppressant medications… would be beneficial." Dr. Patel recommended MRIs of the lower spine (which were performed and had normal findings), pain management, and following up with Dr. Messner to discuss physical therapy and petitioner's request for referral to an immunologist. Pet. Ex. 2 at 148-51.

Afterwards, multiple medical providers at Kaiser Permanente followed Dr. Patel's history and assessment of myofascial pain syndrome. For example, on April 25, 2013, rheumatologist Dr. Pradipta Ghosh "review[ed] excellent note by Dr. Patel for full recent history of present illness" and "agree[d] with Dr. Patel that [myofascial pain syndrome] is the predominant

[20] Piroxicam (referred to in the medical records by the trademark name Feldene) is "a non-steroidal anti-inflammatory drug used for treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis" and other conditions. *Dorland's* at 1451, *see also id.* at 687. Of note, upon prescribing this medication, Dr. Messner recorded that there was "no evidence for… an inflammatory condition." Pet. Ex. 2 at 132.

diagnosis." Pet. Ex. 2 at 172-73. Dr. Ghosh recommended tapering off gabapentin and trying a combination of pregabalin[21] and venlafaxine.[22]

Petitioner averred that throughout this time, he continued working, but only had a few good hours each day. His employer was very tolerant about his lack of performance. After a work day, when he returned home, he would take a two- to three- hour nap to help ease the pain. He was less able to play with his three children and help with their homework. Also in 2013, he had to sell the four rental apartments because he was unable to maintain his responsibilities as a landlord. His family also sold the house in which they were living and bought a different house that was more manageable. Pet. Ex. 3 at 4-5.

Petitioner averred that he started riding motorcycles in 1986. After the June 1, 2012 Tdap vaccination, he had pain and fatigue particularly in his lower extremities which made it difficult to use the foot brakes. Therefore, he accommodated by using only the front (hand) brakes. He knew this carried risks but he did not want to give up motorcycle riding because it alleviated his stress. Pet. Ex. 3 at 5.

On July 26, 2013, petitioner presented to the emergency room at Kaiser Permanente Santa Clara Medical Center ("KPSCMC") following a motorcycle accident. He was exiting the freeway using only the front brakes when they locked. The motorcycle fell onto his left leg. At the hospital, X-rays confirmed fractures in the left tibial plateau, proximal tibia, and fibula. At least two medical providers at the hospital recorded petitioner's report that he had been diagnosed with GBS in 2012. However, the hospital providers adopted Dr. Patel's assessment of myofascial pain. Petitioner underwent surgery to correct the fractures in his left leg. On July 29, 2013, petitioner was discharged with morphine and oxycodone for pain. He was to wear a knee immobilizer as well as crutches or a walker full-time for six weeks. He would also receive physical therapy sessions at home. Pet. Ex. 2 at 195-96, 280-84.

The orthopedic surgeon who performed petitioner's leg surgery excused him from work full-time. Petitioner started to receive disability payments from the State of California. The orthopedic surgeon authorized petitioner to resume work up to four hours per day starting September 23, 2013. Pet. Ex. 2 at 418-19, 438-39.

During an October 22, 2013 appointment with Dr. Messner, petitioner's chief complaint was hypertension associated with poor exercise and diet since the motorcycle accident. Pet. Ex. 2 at 420-21. On February 2, 2014, in an email to Dr. Messner, petitioner stated that after fracturing his leg, he was at home resting a lot, not moving, and taking his "GBS meds" three times a day. After his leg healed, he became more active, went back to work, and lowered the medications. (My impression is that petitioner is talking about decreasing gabapentin, which he could not take during the work day because of its sedative effect.) At that point, his "Guillain-

[21] Pregabalin (referred to in the medical records by the brand name Lyrica) is a treatment for neuropathic pain. *Dorland's* at 1509, *see also id.* at 1088.

[22] Venlafaxine (referred to in the medical records by the brand name Effexor) is "a serotonin norepinephrine-reuptake inhibitor; used as an antidepressant and antianxiety agent." *Dorland's* at 2046, *see also id.* at 595.

Barré symptoms came back with a vengeance. The pain level and weakness was [sic] very high." Pet. Ex. 2 at 441. Petitioner also stated that his "GBS" symptoms were associated with increased blood pressure fluctuations, headaches, and nausea. Dr. Messner suggested increasing gabapentin and adding venlafaxine. Controlling his pain would likely lessen the fluctuations in blood pressure. Pet. Ex. 2 at 441-42.

On February 10, 2014, the orthopedic surgeon authorized petitioner to resume work full-time. Pet. Ex. 2 at 451-52. On February 11, 2014, Dr. Messner prescribed venlafaxine starting at 25 mg per day, increasing to 75 mg per day as tolerated. He also recommended pain management. Pet. Ex. 2 at 453-63. On February 20, 2014, petitioner returned to Dr. Messner complaining of headaches and blood pressure fluctuations. Dr. Messner prescribed clonidine[23] but also stressed that petitioner should "retry" venlafaxine. Pet. Ex. 2 at 464-72. On April 1, 2014, Dr. Messner recorded that petitioner's neuropathic pain was "much better controlled" by an increased dosage of gabapentin supplemented with venlafaxine at 75 mg per day. Dr. Messner again recommended pain management. Pet. Ex. 2 at 492-96.

On May 20, 2014, Dr. Messner recorded that petitioner "did have reaction to Tdap in 2012." He was "thought to possibly have a Guillain-Barré type reaction, but on further testing, no objective evidence for this was noted." Petitioner continued to have "small fiber nerve type pains throughout, mostly lower ext[remities.] But also upper ext[remities]." Petitioner felt okay each morning but developed full body pains and fatigue. Because of that pain, petitioner was thinking of leaving his job and applying for disability. "Extensive rheumatology/ neuro evals neg for any reversible pathology or overt cns/ rheum path." Thus, Dr. Messner adopted the second neurologist Dr. Patel's assessment of myofascial pain syndrome. Petitioner wanted "another opinion re: his pains and his ability to work/function." Dr. Messner recommended pain management and physical therapy. Pet. Ex. 2 at 501-08.

In June 2014, petitioner had an initial consult with a physical therapist who discussed that even if the cause of his chronic pain remained unknown, he needed to accept the diagnosis and learn to live with it. Pet. Ex. 2 at 530-35. In July 2014, petitioner met with a pain management specialist, who recorded that he was "willing to try" a pain management rehabilitation program, but he was "skeptical approach will be helpful and also still has medical concerns about diagnosis." Pet. Ex. 2 at 546-53.

As part of the pain management workup, in August 2014, petitioner met with a psychologist who recorded that he still had pain, tingling and numbness in the hands and feet, weakness in the hands and feet, muscle weakness, and fatigue. Petitioner and his physicians were still "not clear on his diagnosis". Petitioner was unclear how the pain management program would "reverse his nerve damage" and would likely "have great difficulty accepting his pain status and these practices until he understands and has more of an explanation than has been provided thus far." Petitioner was distrustful of the providers at Kaiser Permanente and was exploring legal action concerning the Tdap vaccine. The psychologist referred petitioner to a chronic pain education class. Pet. Ex. 2 at 554-57. However, it does not appear that petitioner went to that class or had any further meetings with pain management specialists.

[23] Clonidine is a treatment for various conditions including hypertension and anxiety. *Dorland's* at 373.

In December 2014, Dr. Messner recorded that petitioner was going to stop working because of his persisting symptoms. Pet. Ex. 5 at 26-30, 38-39. Dr. Messner then completed a "work status report" providing that in June 2012, petitioner had the onset of "neuropathic pain, chronic fatigue syndrome, late effect of Guillain-Barré syndrome" and that as of February 2, 2015, he was placed off work. Dr. Messner also signed petitioner's claim for disability insurance benefits from the State of California. Pet. Ex. 6.[24]

On February 25, 2015 at approximately 3:00 a.m., petitioner presented to the emergency room at KPSCMC with complaints of high blood pressure, headache, and nausea. His blood pressure had stabilized and an EKG was normal. He was discharged to follow up with Dr. Messner. Pet. Ex. 5 at 89-117. The following day, Dr. Messner recorded that petitioner's blood pressure spikes and associated symptoms occurred when he was "under more stress." Pet. Ex. 5 at 118-28.

On March 14, 2015, petitioner returned to his original neurologist Dr. Cho, who recorded that he consistently had muscle fatigue and pain throughout his body. "His symptoms never goes [sic] away but he feels there are times when they are worse – 'flare ups.'" These "flare ups" tended to begin with a bitter taste in his mouth, more burning pain in his feet, and more muscle fatigue, followed by blood pressure fluctuations, headaches, nausea, and dizziness. On physical examination, Dr. Cho recorded normal reflexes and decreased pin prick sensation. Dr. Cho did "not feel his symptoms are from dtap at this time" and did "not feel he has gbs or cidp." However, Dr. Cho "proceed[ed] with further work up for neuromuscular disorder such as painful, sensory motor neuropathies with autonomic involvement." Dr. Cho declined petitioner's request for a muscle biopsy, in favor of follow-up EMG/NCS and bloodwork (which did not have significant findings). Pet. Ex. 5 at 136-39, 143.

On April 28, 2015, Dr. Messner recorded that petitioner's symptoms were worse "when he's been active" and "when he exerts self." Pet. Ex. 5 at 164-67.

In May 2015, petitioner contacted both Dr. Messner and Dr. Cho. Petitioner wanted their written acknowledgment that the Tdap vaccine had caused a sensory form of GBS. He also asserted that he should have received IVIg treatment at the outset, that their failure to order IVIg made his GBS "chronic", and that he still wanted IVIg treatment. Pet. Ex. 9 at 3-5, 10.[25]

In response, Dr. Messner wrote a letter "to whom it may concern," describing petitioner's symptoms which began after the vaccination. "The initial working diagnosis was a Guillain-Barré type of process/ illness," but because his symptoms were "primarily pain and sensory dysesthesias," he was not given IVIg early on. Dr. Messner wrote that petitioner's condition was "consistent with a painful sensory motor neuropathic process/ neuropathy"; "[a]lthough no

[24] This paperwork was also signed by a Dr. James Lin, an emergency room physician at Kaiser Permanente Santa Clara Medical Center. He is described as a treating physician, however, he is not listed in the medical records filed in this case. His involvement in petitioner's medical care and/or personal life is unclear.

[25] The early post-vaccination medical records reflect that petitioner was concerned about GBS. Additionally, he filed this petition in the Vaccine Program on March 19, 2015. It seems more likely than not that petitioner requested these letters at least in part to support his vaccine claim.

longer in the acute phase, a Guillain-Barré precipitated process remains possible." The evaluation was ongoing. Pet. Ex. 8.

Dr. Cho wrote a shorter letter, in which she described the symptoms which began after the vaccine and had continued to the point of being disabling. Dr. Cho's initial impression was that petitioner experienced a "dysimmune syndrome related to the vaccination." Dr. Cho did not provide her current impression. Pet. Ex. 7.

Also in May 2015, petitioner made another late-night presentation to the KPSCMC emergency room, this time for chest pain. Pet. Ex. 9 at 27-52. He was discharged to follow up with Dr. Messner, whose assessment was esophageal spasm in the setting of gastroesophageal reflux disease (GERD).[26] Pet. Ex. 9 at 54-60.

Petitioner was frustrated about his lack of diagnosis and continued symptoms. Dr. Messner suggested further work-up at Redwood City Medical Center, also within the Kaiser Permanente network, which petitioner declined. Petitioner was willing to go outside of Kaiser Permanente and pay out-of-pocket for a second opinion. He found a doctor who had "experience with GBS disorders" at the Palo Alto Medical Foundation. Pet. Ex. 9 at 20, 23-24. However, they turned down his case. Pet. Ex. 9 at 62.

In June 2015, petitioner secured a consultation with Dr. Mitchell Miglis, a neurologist at Stanford University Health Care. Dr. Miglis recorded: "While he has signs and symptoms that are somewhat consistent with an immune-mediated disorder, his serology is negative and thus I do not feel that his current presentation warrants treatment with IVIg and steroids." Dr. Miglis referred to colleagues specializing in neuromuscular conditions with the recommendation of a single fiber EMG.[27] Pet. Ex. 10 at 1-5.

In November 2015, Dr. Srikanth Muppidi, a neurologist in the Neuromuscular/ Autonomic Clinic at Stanford, had an initial consult with petitioner. Dr. Muppidi recorded that petitioner mainly had sensory symptoms and pain. He also recommended a single fiber EMG. Pet. Ex. 12 at 8-12.

In February 2016, Dr. Safwan Jaradeh, another neurologist at Stanford, conducted the single fiber EMG. He recorded: "The study [did] not show evidence for a neuromuscular transmission disorder. Testing for small nerve fiber function (QSART or TST) may provide additional information." The post-procedure diagnoses were fatigue, polyradiculitis, and small fiber neuropathy. Pet. Ex. 17 at 1-13.

[26] GERD involves chronic "backwards or return flow" of the stomach into the esophagus. The principal characteristics are heartburn and regurgitation. *Dorland's* at 533, 616.

[27] Single fiber EMG "use[es] a needle electrode to record the action potential of one muscle fiber at a time." *Dorland's* at 602.

In May 2016, Dr. Muppidi recorded that petitioner's ongoing neuropathic pain likely represented "small fiber neuropathy, which can be confirmed with QSART and skin biopsy." However, confirmation of that condition might not change the treatment options. Pet. Ex. 17 at 15-23. In June 2016, Dr. Muppidi conducted the QSART test, which he recorded was "suggestive of small fiber neuropathy." Pet. Ex. 17 at 31-34. Petitioner asked for IVIg. Dr. Muppidi did not see data to support treatment of petitioner's symptoms with IVIg. Dr. Muppidi and petitioner planned to also pursue a skin biopsy. Pet. Ex. 17 at 36-56.

These outside consultations were reviewed by petitioner's primary care provider at Kaiser Permanente, Dr. Messner. Pet. Ex. 16 at 17-29, 65-73. In July 2016, Dr. Messner emailed petitioner: "The derm dept and neurology dept. are looking into the biopsy for the small fiber neuropathy, as it's not a common procedure." Pet. Ex. 16 at 104. In August 2016, Dr. Messner recorded that the Kaiser Permanente neurology and dermatology department did not feel that a small fiber biopsy would be "of much clinical benefit." Petitioner was frustrated and wanted "a non-Santa Clara Kaiser neuro opinion." Pet. Ex. 16 at 112-22. Afterwards, petitioner had an initial consult with Dr. Edwin Gutierrez, a neurologist at Redwood City Medical Center, also within Kaiser Permanente. Petitioner's chief complaint was that he wanted a skin biopsy. After reviewing the records to date and conducting his own examination, Dr. Gutierrez recorded:

> Although patient may have had neuropathic pain due to exposure to Tdap vaccine (probable small fiber neuropathy by QSART test), I agree with Dr. Patel that the overall picture suggests fibromyalgia/ myofacial [sic] pain syndrome. I don't see any evidence of peripheral neuropathy secondary to GBS or CIDP.

Dr. Gutierrez declined to order a skin biopsy because the findings might not change the treatment plan and he did not see evidence of "progressive peripheral neuropathy." Pet. Ex. 16 at 166-77.

Petitioner paid out-of-pocket for the skin biopsy. Pet. Ex. 17 at 49-50, 54. The samples were obtained at Stanford and sent to Therapath Neurology, a private laboratory in New York. Pet. Ex. 17 at 57-61; Pet. Ex. 18. Analysis of the samples revealed that petitioner's left distal arm had "low normal epidermal nerve fiber density." His left proximal arm, left foot, and right calf all had "significantly reduced epidermal nerve fiber density, consistent with small fiber neuropathy." Pet. Ex. 18 at 2. The skin biopsy report includes the following explanation of small fiber neuropathy, which mirrors petitioner's clinical picture beginning in June 2012:

> Small fiber neuropathies can be length-dependent or non-length dependent which includes multifocal disorders. Length-dependent neuropathies usually begin in the feet with loss of sensation in a stocking distribution in the lower extremities. When the condition is more advanced, a glove-like loss in the upper extremities may also occur. Occasionally, patients with a length-dependent neuropathy can feel symptoms in the hands before the lower extremities. In non-length dependent neuropathies, symptoms may involve the trunk, face, arms, upper extremities, proximal limbs, and other focal areas.

Id. at 3. On September 8, 2016, Dr. Muppidi called petitioner and sent him the results of the skin biopsy. Pet. Ex. 17 at 62-66. It does not appear that they had any further appointments although on October 30, 2016, petitioner emailed about another "flare up" and Dr. Muppidi recommended consistent treatment with gabapentin and pregabalin, plus pain management. Pet. Ex. 20 at 1.

On October 31, 2016, petitioner returned to Dr. Messner, who was the first to record that petitioner had an "*idiopathic* small fiber neuropathy". Pet. Ex. 19 at 76 (emphasis added). Dr. Messner forwarded his encounter records and "review[ed] things" with Dr. Cho, the first neurologist to see petitioner shortly after the Tdap vaccine and onset of symptoms in June 2012. However, Dr. Cho did not have any further appointments or email correspondence with petitioner. Dr. Messner and Dr. Cho referred petitioner to Dr. Amir Sabouri, a neuromuscular specialist within Kaiser Permanente. Pet. Ex. 19 at 25, 76, 94, 98; Pet. Ex. 21 at 45-46.

At his initial consult in January 2017, Dr. Sabouri recorded petitioner's history including that his problems started after a vaccination in 2012. However, Dr. Sabouri did not record any opinion about possible vaccine causation. Under "plan", he recorded: "I spent more than 90 minutes to explain pathophysiology and prognosis of idiopathic small fiber neuropathy. Patient was insisting on getting IVIg, I'm aware of some anecdotal isolated case reports from patients and some providers, who reportedly had treated small fiber neuropathy with IVIg infusion, however, I told to the patient that to the best of my knowledge, there is no convincing and reliable evidence that IVIg was going to be helpful in treatment of idiopathic small fiber neuropathy." Dr. Sabouri recommended increasing the daily amount of gabapentin and "stay[ing] on the minimum effective dose… for 6-8 weeks before calling it a failure," hypertension medication, psychotherapy, and improved exercise and diet. Dr. Sabouri recorded that petitioner would "continue the management of his neuropathic pain with his local neurologist Dr. Cho or his primary care provider Dr. M[essner] [sic]." Pet. 21 at 52-55.

Petitioner had further appointments with Dr. Messner, who forwarded the records to Dr. Cho. Petitioner asked Dr. Messner about the status of communications with Dr. Cho. Dr. Cho was "not aware of outside neurologist who might provide [petitioner] another opinion re: his concern of IVIg." Pet. Ex. 21 111, 139, 142. It is notable that Dr. Cho initially endorsed peripheral sensory nerve involvement and a possible GBS variant, but never addressed the eventual objective findings of a small fiber neuropathy.

As of September 2017, petitioner's problem list included "idiopathic small fiber neuropathy" and "neuropathic pain," but not GBS. He was taking medications for neuropathic pain, anxiety, and hypertension. Pet. Ex. 22 at 1-3. His current condition is unknown.

IV. Analysis

A. Nature of Petitioner's Injury

The first issue to be resolved is whether petitioner has a small fiber GBS variant, Joint Pre-Hearing Submission at 2, as asserted by petitioner's expert Dr. Souayah. *See, e.g.*, Pet. Ex. 14; Tr. 3-78; Pet. Post-Hearing Brief at 1. Respondent's expert Dr. Donofrio contended that petitioner did not fit the "typical" clinical picture of GBS; petitioner failed to demonstrate the

existence of a small fiber GBS variant; and that petitioner did not even fit Dr. Souayah's description of a small fiber GBS variant. *See, e.g.*, Resp. Ex. A; Tr. 88-149; Resp. Post-Hearing Brief at 20-27. Respondent contended that if petitioner did not establish that he suffered the injury alleged, petitioner failed to establish any of the *Althen* prongs. *Id.* at 27-36. Accordingly, I find it appropriate to address the nature of petitioner's injury at the outset.

1. Generally

a. "Typical" GBS

GBS generally encompasses an acute injury to the peripheral nervous system, which is believed to be immune-mediated.[28]

Dr. Donofrio argued for a restrictive definition of GBS. Resp. Ex. A at 8; Tr. 104-07, citing primarily to the Brighton Collaborative, *Guillain-Barré syndrome and Fisher syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data*, 29 Vaccine 599 (2011) [Resp. Ex. A-1]. The Brighton group reviewed significant literature on GBS and other peripheral neuropathies in the context of immunization published between 1976 – 2008. It focused on four GBS variants: acute inflammatory demyelinating polyneuropathy ("AIDP"), acute motor axonal neuropathy ("AMAN"), acute motor and sensory neuropathy ("AMSAN"), and Miller-Fisher syndrome.[29]

AIDP is the most common GBS variant seen within the United States. It is characterized pathologically and electro-diagnostically by focal demyelination of motor and sensory nerves. Resp. Ex. A-1 at 4.

Other recognized GBS variants (much less common in the United States) do not involve damage to the myelin coating the nerve fibers, rather, they involve damage to the axons (nerve fibers). Within this category, AMAN primarily affects motor nerves. AMSAN affects both motor and *sensory* nerves. Resp. Ex. A-1 at 4.

The Brighton group offered three levels of diagnostic certainty for GBS (limiting the scope to AIDP, AMAN, and AMSAN). The third, least certain level requires: bilateral AND flaccid weakness of the limbs; decreased or absent deep tendon reflexes in weak limbs; a monophasic illness pattern AND interval between onset and nadir of weakness between 12 hours

[28] The immune-mediated hypothesis is because first, a viral or bacterial illness often precedes the onset of neurological symptoms. Second, research has found evidence for molecular mimicry, i.e., that antibodies produced to attack those foreign antigens can also attack some component of the peripheral nervous system. These subjects will be discussed further under *Althen* prong one, below.

[29] The Vaccine Injury Table creates a presumption of causation for AIDP, AMAN, AMSAN, or Miller-Fisher syndrome with onset within 3 – 42 days after receipt of seasonal influenza vaccine. 42 C.F.R. § 100.3(a)(XIV)(D).

and 28 days AND subsequent clinical plateau[30]; and no identified alternative diagnosis of weakness. Resp. Ex. A-1 at 14.

The Brighton group's second level of certainty requires the same weakness, areflexia, clinical course, and lack of alternative diagnosis plus "CSF total white cell count < 50 cells/ uL (with or without CSF protein elevation above laboratory normal value) OR If CSF not collected or results not available, electrophysiological studies consistent with GBS." Resp. Ex. A-1 at 13.

The first, most certain level requires the same weakness, areflexia, clinical course, and lack of alternative diagnosis plus "electrophysiologic findings consistent with GBS" and "cytoalbuminologic disassociation (i.e., elevation of CSF protein level above laboratory normal value and CSF total white cell count <50 cells/ uL)." Resp. Ex. A-1 at 12.[31]

The Brighton group also offered diagnostic criteria for another GBS variant, Miller-Fisher syndrome ("MFS") which is characterized by a "classic triad" of areflexia, ataxia,[32] and ophthalmoplegia.[33] In some cases, this classic triad is accompanied by limb weakness, which are considered to be GBS-MFS overlaps. MFS also has a monophasic illness pattern and common finding of elevated cerebrospinal fluid (CSF) protein. The electrodiagnostic findings can be either normal or limited to the sensory nerves. Resp. Ex. A-1 at 7.

The Brighton group developed its criteria for the purpose of researching whether different vaccines might cause or contribute to GBS. Thus, the Brighton group only recognized the most "certain" clinical picture of GBS. Dr. Donofrio agreed that the Brighton group only accepted the GBS cases for which there is "the strongest evidence." Tr. 145-46.

The Brighton group recognized that its definitions "may not capture some of the clinical variants that nonetheless may be related and are regarded by others as forms of 'GBS.' However, these variants are considered to be rare and comprise less than 1% of overall GBS cases. Thus, the number of cases missed by these definitions is expected to be low." Resp. Ex. A-1 at 8-9. Additionally, the Brighton group was not concerned with clinical treatment and management of GBS. Tr. 143-47. On that point, Dr. Donofrio noted that in his own clinical practice, he uses Asbury and Cornblath's criteria for diagnosing GBS, published in 1990. Tr. 94.[34]

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[30] The Brighton group added, in a footnote: "The eventual outcome is either *stabilization at nadir* OR subsequent improvement OR death." Resp. Ex. A-1 at 15 (emphasis added).

[31] The Brighton group added, in a footnote: "CSF may be 'normal' in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently 'normal' CSF, or CSF with >5 WBC, will not meet Level 1 criteria." Resp. Ex. A-1 at 15.

[32] "Failure of muscular coordination; irregularity of muscular action." *Dorland's* at 170.

[33] "Paralysis of the eye muscles." *Dorland's* at 1329.

[34] A. Asbury & D.R. Cornblath, *Assessment of Current Diagnostic Criteria for Guillain-Barré syndrome*, 27 Ann. Neurol. S21 (1990) [Resp. Ex. C].

b. Additional GBS Variants

In contrast to Dr. Donofrio, Dr. Souayah opined that GBS is an "umbrella" term encompassing immune-mediated injury to different aspects of the peripheral nervous system, which will result in different symptoms and diagnostic findings. Tr. 14.

Dr. Souayah submitted considerable medical literature on the continued research of GBS. For example, a 2001 article provided that "the real nosological[35] limits of GBS remain unclear."[36] A more recent article provided that it is "increasingly clear that GBS is not a single entity, but rather a clinically and pathologically heterogeneous group of neuropathic conditions. A number of variants are characterized by localized or regional involvement of the peripheral and autonomic nerves."[37]

Asbury and Cornblath's diagnostic criteria for GBS (which Dr. Donofrio uses in his clinical practice) excludes a "purely sensory syndrome." Resp. Ex. C at S22. These criteria were published in 1990. In 2005, Cornblath and a different coauthor recognized that an "acute sensory neuropathy" may be included in the spectrum of GBS.[38] This has been contemplated by other authors as well.[39]

Because GBS is understood to be an immune-mediated disease, immune-modulatory treatment is indicated. The most common treatments are intravenous immunoglobulin therapy ("IVIg") and plasma exchange ("PE"). Both are associated with better outcomes. Dr. Souayah and Dr. Donofrio agreed that patients with GBS should receive IVIG and/ or PE within the first few weeks. Tr. 34, 94. On cross-examination, Dr. Donofrio agreed that "early use of IVIg or plasma exchange… adequate treatment of neuropathic pain… and appropriate physical and occupational therapy" would reduce the severity and/or duration of GBS residual symptoms. Tr. 137. The medical literature also reflects that if the diagnosis of GBS is delayed, starting treatment at a later point may still be appropriate, particularly if the symptoms are progressing. Thus, from a clinical perspective, it is important to recognize atypical GBS cases so they can receive the appropriate treatment.[40]

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[35] Nosology is "the science of the classification of diseases." *Dorland's* at 1292.

[36] V. Govoni and E. Granieri, *Epidemiology of the Guillain-Barré syndrome*, 14 Curr. Opin. Neurol. 605 (2001) [Pet. Ex. 14-EE] at 608.

[37] J.J. Li et al., Clinical Variants of *Guillain-Barré syndrome in Children*, 47 Pediatr. Neurol. 91 (2012) [Pet. Ex. 14-ZZ] at 95.

[38] R.A. Hughes and D.R. Cornblath, *Guillain-Barré syndrome*, 366 Lancet 1653 (2005) [Pet. Ex. 14-JJ].

[39] *See, e.g.*, A. Uncini and N. Yuki, *Sensory Guillain-Barré syndrome and Related Disorders: An Attempt at Systemization*, 45 Muscle Nerve 464 (2012) [Pet. Ex. 14-OOOO]; H.J. Willison et al., *Guillain-Barré syndrome*, Lancet, pii:S0140-6736(16) 00339-1 (2016) [Pet. Ex. 14-UUUU].

[40] Brighton Collaborative (2011) [Resp. Ex. A-1] at 7; V. Ansar and N. Valadi, *Guillain- Barré syndrome*, 42 Prim. Care 189 (2015) [Pet. Ex. 14-F] at 192; A. Creange, *A Role for Interferon-Beta in Guillain- Barré syndrome?*, 14 BioDrugs 1 (2000) [Pet. Ex. 14-O] at 2; M.M. Dimachkie and R.J. Barohn, *Guillain- Barré syndrome and its Variants*, 31 Neurol. Clin. 491 (2013) [Pet. Ex. 14-Q] at 491; Li et al. (2012) [Pet. Ex. 14-ZZ] at 96.

Dr. Souayah opined that in GBS, "most of the clinical focus is on the motor progression and on the autonomic dysfunction." Pet. Ex. 14 at 22. But GBS frequently also involves pain, both during the initial acute episode and as a later residual symptom. *Id.* This pain can be "severe and disabling." *Id.* This pain can point to damage to small nerve fibers.

Dr. Souayah submitted a 2010 study by Martinez et al.,[41] who explained that GBS is an acute peripheral neuropathy that is traditionally considered to affect "large-diameter myelinated fibers." Pet. Ex. 14-CCC at 53. Although GBS "most commonly manifests as areflexic paralysis, 55 – 85% of patients with GBS report pain, particularly NP [neuropathic pain] affecting the distal extremities. This type of pain my be particularly distressing[.]" *Id.* More recent research has found that GBS "not only affects large myelinated fibers but also impairs small myelinated and unmyelinated fibers." *Id.* Martinez et al. hypothesized that "small fiber dysfunction rather than large fiber lesion may account for acute [neuropathic pain] in GBS and its maintenance over time in a subgroup of patients." *Id.*

Accordingly, Martinez et al. recruited 30 adult patients who met Asbury and Cornblath's diagnostic criteria for GBS upon initial presentation to one hospital. *Id.* at 54. The patients were asked to assess their sensory symptoms including paresthesia, dysesthesia, and pain within days of admission and again 6 and 18 months thereafter. *Id.* They also underwent EMG, NCS, and quantitative sensory testing ("QST") at the same time periods. *Id.* Many of these patients with GBS were found to have afferent small fiber damage at initial presentation, which was positively correlated with neuropathic pain, "generally described as burning, deep or paroxysmal, associated with dysesthesia and predominated distally in the feet." *Id.* at 58. More than half of the patients with neuropathic pain still had it after 18 months. Neuropathic pain "necessitated treatment with antiepileptics or antidepressants in five cases and was responsible for three patients being unable to return to work." *Id.* at 56. These findings reflect that "chronic NP [neuropathic pain] in GBS should be better recognized and managed, as it may contribute further to the disability of these patients." *Id.* at 58. A commentary in the same journal issue summarized that the "impairment of afferent small fiber function…. positively correlated with the burning pain intensity that occurs in the acute phase of the disease and the deficit predicted the persistence of neuropathic pain in its later course… establish[ing] that GBS can manifest not only as an acute condition, but also in many patients as a chronic neuropathic pain syndrome."[42]

Dr. Souayah also submitted a 2012 study by Ruts et al.[43] who described GBS as "an acute immune-mediated disorder of the peripheral nervous system. Its clinical spectrum at the acute phase and its outcome are highly variable." Pet. Ex. 14-WWWW at 399. GBS mainly affects large fibers "carrying motor functions, vibratory, and touch sensation," which "reflects the main clinical features, namely rapidly progressive weakness of the limbs". *Id.* However, GBS

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[41] V. Martinez et al., *Small Fiber Impairment Predicts Neuropathic Pain in Guillain- Barré syndrome*, 151 Pain 53 (2010) [Pet. Ex. 14-CCC].

[42] *See also* A. Binder & R. Baron, *Size Matters – Small Fiber Neuropathy in the Guillain-Barré syndrome*, 151 Pain 9 (2010) [Pet. Ex. 14-H] (praising the study by Martinez et al.).

[43] L. Ruts et al., *Pain in Guillain-Barré syndrome: A Long-Term Follow-Up Study*, 75 Neurology 1439 (2010) [Pet. Ex. 14-UUU].

patients also report acute and long-term neuropathic pain. Ruts et al. recruited 24 adult patients who met Asbury & Cornblath's criteria for GBS and MFS upon initial presentation to various hospitals in the Netherlands. *Id.* The patients' GBS disability score (based on their ability to walk unassisted) was recorded. Additionally, at the acute phase of the disease and after six months, the patients were asked to assess their own pain. *Id.* at 400. At those same intervals, the patients underwent skin biopsy. *Id.* Ruts et al. explained:

> Skin biopsy allows the investigation of small nerve fibers at the pathological level and the quantification of intraepidermal nerve fiber density ("IENFD") which are unmyelinated axons with functions of thermal and nociceptive transduction. Their loss has been found to correlate with symptoms of small fiber neuropathy and patients' quality of life. Studies in peripheral neuropathies of different etiology suggested that intraepidermal nerve fiber ("IENF") degeneration increases the risk of developing neuropathic pain, whereas IENF regeneration is associated with its recovery.

Id. at 399-400. Ruts et al. summarized their results as follows:

> Our prospective study confirmed that small nerve fibers are affected in patients with GBS and MFS since the acute phase of the disease. We showed that a low IENFD in the acute phase was associated with a higher risk to develop neuropathic pain and correlated with its intensity, even in the patients with the pure motor variant… Skin biopsy is a safe technique, and it can be repeated at multiple sites over the course of the disease. Our findings strengthen its potential role in the investigation of the neuropathological changes in GBS and related immune-mediated neuropathies.

Id. at 404.

Dr. Souayah opined that numerous articles have reported "[a]cute small fiber sensory neuropathy as a *primary* manifestation of GBS." Pet. Ex. 14 at 9 (emphasis added). For example, in 2002, Seneviratne and Gunasekara[44] reported on six patients presenting to a hospital in India with "acute onset peripheral sensory neuropathy." All six had normal strength and reflexes. Additionally, all six had "acute onset numbness of the upper and lower limbs. One patient complained of numbness over the face as well. Four had associated burning dysesthesia in the limbs." Pet. Ex. 14-BBBB at 540. All six patients had elevated CSF protein (measured from one to four weeks after the onset of symptoms), but normal motor and sensory EMG/NCS results which would exclude demyelinating neuropathy (such as AIDP) or axonal neuropathy (such as AMAN and AMSAN). *Id.* at 541-42. They had a relatively good recovery without immune-modulating treatment within six months; their pain generally subsided before the numbness did. *Id.* at 542. There was no further electrophysiological testing, such as QSART or skin biopsy, to confirm the existence of small fiber damage. However: "The overall clinical picture along with electrophysiological findings is in favor of selective involvement of small

[44] U. Senevirante & S. Gunasekara, *Acute Small Fiber Neuropathy: Another Variant of Guillain- Barré syndrome?*, 72 J. Neurol. Neurosurg. Psychiatry, 540 (2002) [Pet. Ex. 14-BBBB].

diameter sensory fibers with relative sparing of large myelinated fibers and small sympathetic fibers in the group." *Id.* at 542. Seneviratne and Gunasekara considered these patients to represent a subgroup of sensory GBS, which they termed acute small fiber sensory neuropathy (ASFSN). *Id.*; *see also* 540 (abstract).

In 2014, Makonahalli et al.[45] reported on one patient who contracted a viral infection and subsequently developed facial palsy and a distal burning sensation in all four extremities. Pet. Ex. 14-AAA at 147. Upon presentation to an Australian hospital, "[s]ensory examination in the upper and lower limbs revealed diminished pinprick sensation in the glove and stocking distribution with preserved proprioception and vibration." *Id.* at 147-48. Autonomic function was mildly impaired. *Id.* at 148. Strength, reflexes, EMG, and NCS were normal. *Id.* The patient was found to have elevated mycoplasma IgM antibody titer and elevated CSF protein (approximately two weeks after exposure to the viral antigen). *Id.* at 148. The patient received IVIg during the acute phase of the illness; all symptoms had resolved by six months later. *Id.* Makonahalli et al.'s assessment was an acute, monophasic small fiber neuropathy. *Id.* Because of the elevated CSF protein approximately two weeks after exposure to viral infection and improvement following IVIg, this should be considered a GBS variant. *Id.* at 149. Makonahalli et al. concluded by emphasizing "the importance of prompt diagnosis and appropriate treatment of rare variants of GBS to ensure optimum recovery." Id. at 149. Indeed, this is a common theme in the literature. As discussed above, the experts agreed that GBS should be treated with immunomodulatory treatment quickly and in the acute phase to improve outcomes.

c. Small Fiber Neuropathy

The experts did not file any literature simply explaining the anatomy and symptoms of small fiber neuropathy. I observed that the pathology report from petitioner's skin biopsy in 2016 (Pet. Ex. 18) cited two articles on small fiber neuropathy. These are introduced as Court's Exhibits 1-2.[46] In a 2009 article published in the Cleveland Clinic Journal of Medicine, two neuromuscular specialists, Tavee and Zhou wrote that small fiber neuropathy is damage to the "peripheral nerves that primarily or exclusively affects small somatic fibers, autonomic fibers, *or both*". Ct. Ex. 1 at 297-98 (emphasis added). "Damage to or loss of small somatic nerve fibers results in pain, burning, tingling, or numbness that typically affects the limbs in a distal-to-proximal gradient." *Id.* at 298. "*When* autonomic fibers are affected, patients may experience dry eyes, dry mouth, orthostatic dizziness" and other symptoms. *Id.* (emphasis added). "Motor strength, tendon reflexes, and proprioception, however, are preserved because they are functions of large nerve fibers." *Id.* at 297-98; *see also* Tr. 15-16 (Dr. Souayah's more concise explanation).

[45] R. Makonahalli et al., *Acute Small Fiber Neuropathy following Mycoplasma Infection: A Rare Variant of Guillain-Barré syndrome*, 15 J. Clin. Neuromusc. Dis. 147 (2014) [Pet. Ex. 14-AAA].

[46] J. Tavee and L. Zhou, *Small Fiber Neuropathy: A Burning Problem*, 76 Cleve. Clin. J. Med. 297 (2009) [Ct. Ex. 1]; S.T. Hsieh, *Pathology and Functional Diagnosis of Small Fiber Painful Neuropathy*, 19 Acta Neurol. Taiwan 82 (2010) [Ct. Ex. 2].

Routine EMG and NCS only assess the function of large fibers. Ct. Ex. 1 at 301; Ct. Ex. 2 at 82-83. More specific tests are needed to assess small fibers. One method is QSART, which requires "specialized equipment and must be performed on site. In addition, the test is very sensitive to drugs that can affect sweating, such as antihistamines and antidepressants, and such drugs must be discontinued 48 hours before the study." Ct. Ex. 1 at 301-02.

Dr. Souayah and Dr. Donofrio agreed that the "gold standard" for confirming small fiber neuropathy is skin biopsy. Tr. 69, 108. This is more sensitive than quantitative sensory testing (used by Martinez et al. to measure small fiber damage in GBS patients, as discussed above). Skin biopsy is not widely available. While treating providers can obtain the samples, they need appropriate training to avoid damage to the epidermis. There are only a few laboratories in the United States to process the samples. *Id.* at 301-02.

Small fiber neuropathy has a number of possible causes. The most common is diabetes; others include toxic exposure, vitamin deficiencies, and rare hereditary conditions such as Fabry disease and Tangier disease. Tr. 33-34, 110; Ct. Ex. 1 at 300; Ct. Ex. 2 at 83. Small fiber neuropathy can also be immune-mediated. Dr. Donofrio testified that small fiber neuropathy could be caused by "some of the collagen vascular diseases or connective tissue diseases, and they are often immune-modulated" and "rarely can you see a small fiber neuropathy develop after some infectious processes." Tr. 132-33.

Dr. Donofrio is correct that some small fiber neuropathies are currently labeled "idiopathic, meaning we don't know." Tr. 110; *see also* Ct. Ex. 1 at 299 ("Some [small fiber neuropathy] cases, however, are idiopathic"); *Dorland's* at 912 (defining "idiopathic" as "of unknown cause or spontaneous origin").

However, Tavee and Zhou emphasize that "idiopathic" is not an answer; rather, identifying the cause of small fiber neuropathy is key to administering the correct treatment. Ct. Ex. 1 at 303. Additionally, some cases of small fiber neuropathy may be immune-mediated, meaning that they should be treated with IVIg in the early, acute phase. "It has also been reported that treatment of sarcoidosis, *autoimmune diseases,* and celiac disease improved the symptoms of small fiber neuropathy resulting from these conditions. *Id.* at 303 (emphasis added). Dr. Souayah submitted other literature providing that some cases of small fiber neuropathy are responsive to immunomodulation such as IVIg[47] and should be considered a GBS variant.[48] Dr. Souayah even submitted an article describing GBS as a spectrum of "spectrum of clinical conditions in which *idiopathic* peripheral neuropathy causes acute or subacute weakness of limbs and/or cranial nerve-innervated muscles."[49] Thus, the small fiber neuropathy cases currently labeled as "idiopathic" merit further research as to their causes, and by extension, their appropriate treatment.

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[47] V. Bril and H.D. Katzberg, *Acquired Immune Axonal Neuropathies,* 20 Continuum 1261, 1272 (2014) [Pet. Ex. 14-J].

[48] Makonahalli et al. (2014) [Pet. Ex. 14-AAA].

[49] P. Haber et al., *Vaccines and Guillain-Barré syndrome,* 32 Drug Saf. 309, 310 (2009) [Pet. Ex. 14-HH] (emphasis added).

d. Conclusion as to Existence of a "Small Fiber GBS Variant"

As discussed above, GBS describes an immune-mediated, acute peripheral neuropathy. There are several variants, the most common of which is AIDP which involves injury to myelin encasing the large-diameter nerve fibers and results in decreased motor function. Less common are AMAN and AMSAN, in which the injury is not to myelin, but to the nerve fibers themselves. AMAN is limited to motor nerves, while AMSAN involves both motor and sensory nerves. The Brighton Group has restrictive criteria intended to capture the "strongest," most "certain" cases of GBS for purposes of researching possible vaccine causation. Regardless, the medical community continues to propose additional peripheral neuropathies that might constitute variants of GBS. Recognizing these cases as GBS variants may result in early immune-modulating treatment, which may result in better outcomes for those patients.

Dr. Souayah also explained that within the GBS "umbrella," motor dysfunction is observable to the naked eye and measurable on neurologic exam and routine EMG/NCS studies. There is increasing recognition that even patients with "typical" GBS (i.e., presenting with motor and autonomic dysfunction and elevated CSF protein) also experience sensory symptoms, including pain. These symptoms can be both acute and chronic. Recent literature such as the 2010 article by Martinez et al. and the 2012 article by Ruts et al. indicate that even patients with "typical" GBS can suffer small fiber damage, which correlates with chronic pain.

Additionally, a few articles have proposed a GBS variant primarily affecting the small fibers. Small fibers cannot be assessed on routine EMG/ NCS, but only on more sensitive tests such as QSART and skin biopsy, which are not widely available even within the United States.

Small fiber neuropathy has various causes, some of which are autoimmune. If all currently identified causes are ruled out, a case of small fiber neuropathy may be labelled "idiopathic." However, that term indicates the *lack* of a known cause. The literature reflects that for small fiber neuropathy, like GBS, understanding and proper treatment of the condition is paramount.

The expert reports, testimony, and medical literature reflect that the nosology of peripheral neuropathies, including the immune-mediated ones falling under the umbrella of "GBS", continues to evolve. The literature supports the existence of an immune-mediated small fiber neuropathy, which would manifest with sensory and/or autonomic dysfunction in a stocking-glove pattern. This kind of neuropathy can only be confirmed by more sensitive tests such as QSART and skin biopsy. Ordering those tests upon the patient's initial presentation could confirm the diagnosis of small fiber neuropathy and predict whether the patient might experience chronic pain. The workup would also include ruling out alternative causes for small fiber neuropathy. It would also include confirming an immune-mediated process, as shown by an elevated CSF protein level. (Although the experts agreed that CSF protein can be normal for the first one to two weeks of an immune response.). Thus, I conclude that petitioner has adequately supported the existence of an immune-mediated small fiber neuropathy, which may be referred to as a small fiber GBS variant.

2. Application to Petitioner's Case

The next question to be resolved is whether petitioner's course from 2012 – 2016 resembles a small fiber GBS variant.

a. Before the June 1, 2012 Tdap Vaccination

Dr. Souayah opined that before the vaccine, petitioner was "healthy." Pet. Ex. 14 at 1; Tr. 12. Similarly, Dr. Donofrio did not emphasize any pre-vaccination medical history. Resp. Ex. A at 1. On cross-examination, petitioner's counsel asked Dr. Donofrio whether petitioner was "experiencing neuropathic pain prior to his Tdap vaccine"; Dr. Donofrio responded: "Not that I could find." Tr. 132.[50]

b. Petitioner's Development of Peripheral Sensory Neuropathy After the June 1, 2012 Vaccination

Petitioner first developed pain in the upper left shoulder muscle (where he received the vaccine). He also developed pain and weakness in both forearms and palms. He then developed pain, burning, weakness, and numbness in both lower legs. Petitioner first reported these symptoms seven days after the Tdap vaccine, on June 8, 2012, in an email to his primary care provider Dr. Messner. On June 11, 2012, Dr. Messner recorded these symptoms and observed decreased sensation to pinprick. That same day, a neurologist, Dr. Cho, recorded the same symptoms and decreased sensation, which were in a stocking-glove pattern and consistent with peripheral nervous system involvement. Dr. Cho prescribed gabapentin for these symptoms. Dr. Souayah opined that these symptoms were consistent with a small fiber neuropathy. Tr. 12-15. Dr. Donofrio opined that the "symptoms of burning… ma[de] [him] think of neuropathic pain," Tr. 131, for which gabapentin was an appropriate treatment. Tr. 111-12, 131-32.

Petitioner also developed facial numbness (which was confirmed by Dr. Cho on examination) and a bitter or metallic taste in his mouth. Dr. Souayah opined that these symptoms represented involvement of the fifth, seventh, and ninth cranial nerves. Tr. 12, 16, 38, 73. When asked by respondent's counsel whether this taste could be a symptom of GBS, Dr. Donofrio answered: "In my 35 to 40 years of taking care of these people, I haven't seen it." Tr. 95-96. Upon review, the medical literature establishes that the peripheral nervous system extends to the cranial nerves. Numerous GBS variants including AIDP, AMAN, AMSAN, and

[50] Dr. Donofrio opined that Pet. Ex. 2 at 15-19 constituted records from an appointment with petitioner's primary care provider Dr. Messner for follow-up of an unidentified condition on June 5, 2012. Resp. Ex. A at 1; Tr. 95-96; *see also* Resp. Post-Hearing Brief at 2. To the contrary, these records are petitioner's routine wellness check-up and receipt of the Tdap vaccine on June 1, 2012. The neurological exam – specifically including sensation – was normal. These records reflect that on June 1, 2012, petitioner reported symptoms of carpal tunnel syndrome and restless leg syndrome. The experts did not opine about these symptoms. Without further explanation, I find that these are non-specific and not related to petitioner's post-vaccine injury.

Miller-Fisher syndrome can involve the cranial nerves. Unusual facial and taste sensations have been reported.[51]

c. Possibility of Motor Nerve Involvement

The experts disagreed as to whether petitioner had motor symptoms, particularly diminished reflexes and strength. Dr. Souayah emphasized that petitioner reported weakness and fatigue. Tr. 12. Dr. Donofrio correctly noted that on physical examination, Dr. Messner and Dr. Cho both assessed normal reflexes. Dr. Messner recorded that strength was normal, while Dr. Cho described petitioner's strength as "give-way." Dr. Cho followed up with functional exercises. At Dr. Cho's request, petitioner was able to "complete 10 sit/ stands without using hands" and "get from floor without using hands." Tr. 97-98. I agree with Dr. Donofrio that petitioner's strength and reflexes – controlled by the motor nerves - were minimally, if at all affected. However, I do find it significant that petitioner's movements from sitting to standing, and from floor to standing, "caused pain." This notation further supports that petitioner had small fiber neuropathic pain.

d. Lumbar Puncture

On June 12, 2012, petitioner underwent a lumbar puncture which showed normal CSF. Dr. Souayah opined that this can occur in approximately the first week of GBS. Tr. 28-29.[52] Dr. Donofrio agreed that in GBS cases, "the protein is elevated 80 to 90 percent of the time, and that elevation also depends on the timing of the lumbar puncture." Tr. 93.[53] Petitioner never underwent a repeat lumbar puncture. I find that this normal CSF protein reading eleven days after the Tdap vaccine does not rule out an immune-mediated process.

e. Treating Physicians' Initial Assessments

At petitioner's first presentation for medical attention after the Tdap vaccine, on June 11, 2012, Dr. Messner assessed dysesthesias possibly representing a GBS variant. The first neurologist seen, Dr. Cho, agreed that petitioner had experienced a sequelae to the Tdap vaccine manifesting as "peripheral nerve involvement" that was "mostly sensory." Because petitioner's motor nerves were intact, this represented a "variant of GBS." Dr. Cho believed that petitioner would plateau and then recover without an inpatient workup or IVIg.

f. Petitioner's 2012 Travel to Jordan

Dr. Donofrio found it "odd that petitioner would choose to spend prolonged time in the country of Jordan in the setting of an illness causing him significant weakness and pain." Resp. Ex. A at 8. He opined that a person with neuropathic pain would "not want to travel" and "be

[51] *See, e.g.*, Hughes & Cornblath (2005) [Pet. Ex. 14-JJ]; L. Yu et al., *Multiple Cranial Neuropathies without Limb Involvements: Guillain-Barré variant?*, 37 Ann. Rehab. Med. 740 (2013) [Pet. Ex. 14-XXXX].

[52] A.B. Pithadia & N. Kakadia, *Guillain-Barré syndrome*, 62 Pharmacol. Rep. 220, 226 (2010) [Pet. Ex. 14-NNN].

[53] Citing the Brighton Collaborative (2011) [Resp. Ex. A-1] at 15.

away from the very physicians they needed should they worsen." Tr. 99. Dr. Souayah did not respond on this point. Upon review, the medical records reflect that in late June 2012, Dr. Cho believed that petitioner's symptoms were getting better. He would taper off clonazepam and increase gabapentin on his own, without Dr. Cho's direct supervision. It was "medically safe for him to travel to Jordan (month of Aug)." Pet. Ex. 2 at 109. In his affidavit, petitioner explained that his three children had gone to Jordan at the end of May 2012, to visit their grandparents. In August 2012, petitioner went to join them. His pain continued throughout this trip. Pet. Ex. 3. Petitioner returned to the United States by September 19, 2012, when he had a follow-up appointment with Dr. Messner and underwent an EMG/NCS. Pet. Ex. 2 at 118-20. Thus, petitioner was cleared to travel by his treating neurologist; he could continue treating for neuropathic pain without the neurologist's supervision; and he had compelling reasons to travel to Jordan.[54] This does not indicate that petitioner's neuropathic pain abated.

g. EMG/NCS

The September 2012 EMG/NCS did not show evidence of "large fiber sensorimotor neuropathy." However, Dr. Cho noted that this testing did not assess for small fiber neuropathy. Additionally, over the next few months, petitioner was stable but continued to have pain at 2/10 at the beginning of the day, escalating as high as 10/10 by the end of an active work day. Gabapentin helped but had a sedative effect so he could not take it during the work day. In January 2013, Dr. Messner's assessment remained neuropathic pain. In March 2013, petitioner returned to Dr. Cho, who recorded that petitioner's neurologic exam was not much different than they had been in June 2012, his symptoms had stabilized, but he continued to have neuropathic pain beginning at 2/10 upon waking up. Accordingly, the EMG/NCS did not seem to change the treating physicians' initial assessments. However, Dr. Cho sought a second opinion from another neurologist within Kaiser Permanente.

h. Assessment of Myofascial Pain Syndrome

The second neurologist, Dr. Patel, saw petitioner for the first and only time in March 2013. After reviewing the Kaiser Permanente chart, Dr. Patel wrote that there was a temporal association between the Tdap vaccine and the subsequent onset of symptoms. On neurologic exam, the findings were mainly sensory. Dr. Patel assessed that petitioner had decreased pinprick sensation on both sides of his face and both upper extremities, but apparently normal sensation to his legs. However, Dr. Patel wrote that there were "no objective findings to suggest injury to the nervous system." He did not order the tests – i.e., QSART or skin biopsy – which could detect those objective findings. His assessment was myofascial pain syndrome. This seems to be based in part on certain notations of myofascial pain in 2008 - 2009. While petitioner's "problem list" notes myofascial pain, he did not file the actual records going back that far, respondent did not request them, and the experts did not opine that they were significant. Additionally, the medical records reflect and Dr. Donofrio agreed that petitioner was largely healthy upon receiving the Tdap vaccine in June 2012. I find it difficult to connect these stray

[54] Dr. Donofrio noted that petitioner traveled to Jordan again in summer 2015. Petitioner did not address this in his affidavit, but absent other information, I presume that he visited family again. This does not indicate that petitioner's neuropathic pain abated.

notations of myofascial pain in 2008 – 2009 to petitioner's new condition beginning in June 2012, which was most consistently described and treated as neuropathic pain.

Dr. Souayah and Dr. Donofrio agreed that myofascial pain syndrome involves muscle pain and tenderness, which are not reflected in petitioner's medical records. Tr. 35, 45-46, 52; Resp. Ex. A at 11-12; Tr. 35, 111, 131. Dr. Donofrio added that petitioner consistently took gabapentin which was not a treatment for myofascial pain, but for neuropathic pain. Tr. 131.

i. Motorcycle Riding & Accident

Dr. Donofrio found it "peculiar" that after developing a GBS variant involving neuropathic pain, petitioner continued to ride a motorcycle, at least up until an accident in July 2013. Resp. Ex. A at 8, Tr. 113. As noted above, petitioner's prevailing symptom was neuropathic sensory pain. This began in his upper extremities, but also developed in his feet and lower legs. These were associated with fatigue. However, the fatigue was not the overriding symptom. Additionally, in his affidavit, petitioner averred that he had been riding motorcycles since 1986. After the vaccine, it was difficult to use the foot brakes. He accommodated by using only the front (hand) brakes. He knew this carried risk but he did not want to give up motorcycle riding because it alleviated his stress. Pet. Ex. 3 at 5. In the hospital records, petitioner reported that the accident occurred because he was using only the front brakes upon exiting the freeway. Pet. Ex. 2 at 195-96, 280-84. I find that this is a logical explanation for why and how petitioner continued to ride his motorcycle. It does not indicate that his neuropathic pain abated. Rather, it tends to show that his neuropathic pain persisted and caused him to stop using the foot brakes, which led to the accident.

Dr. Donofrio also asserted that petitioner did not complain of pain, weakness, or fatigue at the hospital. Resp. Ex. A at 8; Tr. 113-17. During the entitlement hearing, I commented that an individual seeking medical attention for an acute injury, such as a broken leg, might provide less detail about a chronic problem, such as pain. Tr. 115-16. Upon review, the hospital records are focused on the broken leg, but also mention petitioner's chronic problems. *See, e.g.*, Pet. Ex. 2 at 188 (petitioner stated that he was diagnosed with GBS since 2012 and he had weakness, decreased sensation, and fatigue); *id.* at 225 (petitioner had chronic pain and was taking gabapentin at night); *id.* at 231 (petitioner stated that he had GBS, weakness in arms and legs, and fatigue).

j. Following the Motorcycle Accident

On July 29, 2013, petitioner was discharged from the hospital to his home. He was to take morphine and oxycodone for pain, wear a knee immobilizer, use crutches or a walker full-time for six weeks, and work with a physical therapist who would visit his home. Additionally, he began receiving disability payments from the State of California after his orthopedic surgeon excused him from work. In late September 2013, the orthopedic surgeon authorized him to work up to four hours per day. In February 2014, Dr. Messner recorded petitioner's report that as his leg healed, he became more active and lowered his "GBS meds" (presumably the gabapentin, which had a sedative effect and petitioner did not like to take during the work day). At that point, petitioner's "Guillain-Barré symptoms came back with a vengeance. The pain level and

weakness was very high." Pet. Ex. 2 at 441. However, on February 10, 2014, the orthopedic surgeon authorized petitioner to return to work full time. Pet. Ex. 2 at 451-52.

k. Additional Symptoms

Dr. Donofrio opined that petitioner had additional symptoms which were not well explained. First, petitioner reported cognitive problems. Tr. 98, 109. The medical records reflect that after petitioner received the Tdap vaccine and developed neuropathic pain, Dr. Cho recorded that the associated stress could impair concentration and memory. Dr. Cho also prescribed clonazepam. Pet. Ex. 2 at 99. Then, Dr. Cho then recorded that clonazepam might be contributing to petitioner's cognitive issues and should be tapered down. *Id.* at 108-10. Additionally, petitioner developed depression for which he was seeing a psychiatrist by January 2013 and for which he took various medications. *See, e.g., id.* at 131. I find that petitioner's physical symptoms, which were difficult to diagnose and treat, contributed to his subsequent cognitive problems.

Dr. Donofrio opined that petitioner also had atypical chest pain and abdominal pain. Tr. 109. The medical records reflect that petitioner was diagnosed with hypertension prior to the Tdap vaccine and onset of neuropathic pain. Afterwards, he had multiple episodes of elevated blood pressure variously associated with headaches, dizziness, chest pain, and stomach pain. In 2015, Dr. Messner recorded that these symptoms were physical manifestations of stress, which petitioner could better manage. He prescribed Ativan to manage these stress episodes when they occurred and recommended that petitioner work with the pain management team. *See, e.g.*, Pet. Ex. 5 at 119, 128. However, the medical records reflect that over the years, petitioner was increasingly frustrated with the Kaiser Permanente medical providers for not giving him a clear diagnosis. He continued to have neuropathic pain and decreased sensation, for which he did not receive effective treatment or objective confirmation. For these reasons, he was not compliant with Kaiser Permanente's recommendations, such as working with a pain management team. He also felt unable to care for his family and keep up with work. I find that petitioner's neuropathic pain led to significant stress which contributed to these episodic blood pressure fluctuations and other physical symptoms.

l. Petitioner's Overall Course

Dr. Donofrio opined that petitioner's course was inconsistent with GBS. "Almost all patients with GBS require hospitalization during the initial few weeks of the illness because of profound weakness and the possibility of respiratory failure." Most patients with GBS have a good recovery. The pain associated with GBS usually abates over a few weeks, does not fluctuate greatly over time, and does not magnify over months to years. In contrast, petitioner was not hospitalized in the early course of his disease; he seemed to have as many as eight "flare-ups", and his condition seemed to worsen over the years to the point that he could no longer work in 2015. Resp. Ex. A at 7-8; Tr. 90-112, 121.

Upon review, Dr. Donofrio's opinion was focused on "typical" GBS involving the motor nerves. The differences he identified are consistent with a small fiber GBS. First, typical GBS often involves hospitalization for weakness and the possibility of respiratory failure because of

motor nerve involvement. They would not be present in a small fiber GBS, such as petitioner's case. That explains why he was not hospitalized.

Next, IVIg is associated with better outcomes. In this case, the first neurologist involved, Dr. Cho, considered but decided against IVIg because petitioner seemed to be "plateauing" on his own. Dr. Cho authorized petitioner to travel to see his family in Jordan and then directed follow-up with the primary care provider Dr. Messner. Dr. Cho did not see petitioner again for nine months, until petitioner complained of persistent symptoms.

Next, compared to motor nerve damage which is most prominent in typical GBS cases, sensory small fiber nerve damage is more persistent and severe, difficult to detect, and challenging to treat. This explains petitioner's long-term course. Namely, petitioner was employed full-time as a mechanical engineer at NASA for over 20 years, he owned and managed four rental properties for supplemental income, and he was married with three children. After the Tdap vaccine and onset of small fiber neuropathy in June 2012, he continued working at NASA but his productivity decreased to only a few good hours each day. His employer was tolerant about his decreased performance. After a work day, he would go home and nap for several hours. He was less able to play with his three children and help with their homework. Additionally, in 2013, he sold the four rental apartments because he was unable to maintain his responsibilities as a landlord. The family also moved to a house that was more manageable. In July 2013, petitioner had a motorcycle accident. The most significant "flare" seemed to be after the motorcycle accident, in later 2013 – early 2014, when he returned to work and lowered his medications. Other flares also correlated with adjustments to his medication. Gabapentin was the most effective at managing his pain, but it had a sedative effect which interfered with work and other responsibilities. Thus, petitioner and his doctors frequently adjusted the dose of gabapentin and added other medications including clonazepam, duloxetine hydrochloride, piroxicam, pregabalin, venlafaxine, and clonidine. The flares also correlated with stress over his life responsibilities (as detailed above) and the lack of objective findings, a clear diagnosis, or effective treatment. As a result, petitioner was less willing to work with pain management specialists and others within Kaiser Permanente. His chronic symptoms and desire for an explanation were associated with stress and depression. In May 2014, Dr. Messner recorded that petitioner was thinking of leaving his job. Dr. Messner again encouraged pain management and physical therapy. After meeting with those specialists, in December 2014, petitioner decided that he would stop working. Dr. Messner submitted a report to the California state employment disability program that petitioner stopped working in February 2015. I find that this long-term course is consistent with a small fiber GBS variant.

m. Confirmation of Small Fiber Neuropathy

In 2016, petitioner finally underwent QSART and a skin biopsy which confirmed small fiber neuropathy. Dr. Donofrio opined that skin biopsy is the "gold standard" for diagnosing small fiber neuropathy. In petitioner's case, he felt that it was a "stretch" to relate the small fiber neuropathy confirmed by the skin biopsy in 2016 back to the Tdap vaccine in June 2012. Tr. 108-10. But he agreed that: "We certainly can't say that if [petitioner] had had the test done in 2012, it wouldn't have been just as positive." *Id.* at 110.

Dr. Donofrio's efforts to separate out these events are unpersuasive. Upon review, in June 2012, petitioner presented with a "stocking-glove" pattern of sensory loss, pain, weakness, and fatigue for which he was started on gabapentin. Dr. Donofrio agreed that these symptoms and treatment were consistent with a neuropathy. Tr. 99, 111-12, 131-32. These are also consistent with the descriptions of small fiber neuropathy in the skin biopsy report and two articles cited therein. Pet. Ex. 18, *citing* Ct. Exs. 1-2. Petitioner continued to experience neuropathic pain for which he consistently took gabapentin and other medications over the next several years. The medical records are complicated by petitioner's sequelae and frustration with the lack of treatment or objective confirmation of his injury. However, the original symptoms are consistent with the skin biopsy's findings and description of small fiber neuropathy.

Dr. Souayah and Dr. Donofrio agreed that the medical records do not reflect any known cause of small fiber neuropathy. Tr. 13, 34, 71-72, 110, 132. Dr. Donofrio testified that he "[didn't] have an explanation as to what caused [his] small fiber neuropathy." Tr. 132. He agreed with the treating providers who recorded that it was "idiopathic." *Id.*

Upon review, in June 2012, Dr. Messner and Dr. Cho recorded that petitioner had symptoms consistent with a peripheral neuropathy, which they linked to the Tdap vaccine. In March 2013, a second neurologist, Dr. Patel, assessed petitioner with myofascial pain because there were no "objective findings to suggest injury to the nervous system" but recognized that his symptoms were largely "sensory." There were no further neurology consultations (excluding the July 2014 hospitalization following the motorcycle accident) until March 2015, when petitioner returned to Dr. Cho. She stated that petitioner's symptoms were not associated with the Tdap vaccine, GBS, or CIDP. Regardless, Dr. Cho proceeded "with further workup for neuromuscular disorder such as painful, sensory motor neuropathies with autonomic involvement." In 2015 – 2016, petitioner went outside of his health insurance network and met with three neurologists at Stanford – Drs. Miglis, Muppidi, and Jaradeh – who obtained objective evidence of small fiber neuropathy. Perhaps if that was obtained earlier in time, the providers might have drawn a connection between the vaccine, initial symptoms, and small fiber neuropathy. They might have ordered IVIg. Petitioner may have had a more limited course.

After petitioner obtained objective evidence of small fiber neuropathy, he never returned to his original neurologist Dr. Cho. Instead, he was referred to a new neurologist within the Kaiser Permanente network, Dr. Gutierrez, who recorded: "Although patient may have had neuropathic pain due to exposure to TDAP vaccine (probable small fiber neuropathy by QSART test), I agree with Dr. Patel that the overall picture suggests fibromyalgia/ myofacial [sic] pain syndrome. I don't see any evidence of peripheral neuropathy secondary to GBS or CIDP." This record is not easy to parse. Dr. Gutierrez seems to link the June 2012 Tdap vaccine to the 2016 QSART finding of small fiber neuropathy, but also accept an *intervening* 2013 assessment of myofascial pain.

Afterwards, in 2017, petitioner returned to Dr. Messner, who introduced the descriptor "idiopathic" small fiber neuropathy. Petitioner was then referred to a neuromuscular specialist, Dr. Sabouri, who "spent more than 90 minutes to explain pathophysiology and prognosis of idiopathic small fiber neuropathy" but did not record that explanation. In my opinion, there are many gaps in the neurological assessments from 2012 – 2017.

The eventual assessment of "idiopathic" small fiber neuropathy does not resolve this case. "Idiopathic" simply means that the cause of the medical condition is unknown. Respondent cannot simply point to an "idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor" to explain petitioner's condition. § 13(a)(2).

B. *Althen* Prong One: Petitioner's Theory

1. Legal Standard

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. The theory still must be based on a "sound and reliable medical or scientific explanation." *Id.* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (emphasis added).

2. Discussion and Conclusion

Dr. Souayah opined that approximately two-thirds of patients diagnosed with GBS have an antecedent infection within six weeks before the onset of symptoms referable to the peripheral nervous system. The antecedent infection may be viral or bacterial. Although the pathological organism is not often identified, the usual infectious agents include Epstein-Barr virus, *Mycoplasma pneumoniae*, *Campylobacter jejuni* ("*C. jejuni*"), and cytomegalovirus. Pet. Ex. 14 at 10-11,[55] Tr. 90.

Based on the frequency of antecedent infection as well as elevated CSF protein, GBS is believed to be an immune-mediated disorder. The leading theory to explain GBS is molecular mimicry, in which a foreign antigen and a part of the body are nearly identical, which induces an antibody and T cell immune response that is cross-reactive. Pet. Ex. 14 at 11. GBS involves cross-reactivity between the foreign antigen and a part of the peripheral nervous system. Pet. Ex. 14-NNN at 222.

Dr. Souayah opined that the strongest evidence for the molecular mimicry hypothesis has come from discoveries in research with *Campylobacter jejeuni* (*C. jejeuni*) strains. Research has identified an association between antecedent *C. jejeuni* infection and GBS, in particular the AMAN and AMSAN variants. This correlates with findings that antibodies produced against

[55] *Citing* A.B. Pithadia & N. Kadakia, *Guillain-Barré syndrome (GBS)*, 62 Pharmacol. Rep. 220 (2010) [Pet. Ex. 14-NNN].

certain *C. jejuni* antigens can also bind to gangliosides which are concentrated at the nodes of Ranvier.[56] This results in the axonal damage as seen in AMAN and AMSAN. Tr. 32, 64-65.[57]

Dr. Souayah submitted numerous medical articles in support of his theory. Many of which related to various live viruses and vaccines including influenza, hepatitis, and human papillomavirus (HPV). Pet. Ex. 14 at 13-19.[58]

Dr. Souayah extrapolated to opine that Tdap vaccine can also cause molecular mimicry resulting in GBS. He opined that in 1994, the IOM concluded that there was sufficient evidence to suggest causality between tetanus toxoid and GBS based on biologic plausibility and one case report from Pollard and Selby.[59] Pet. Ex. 14 at 19.[60] However, on cross-examination, Dr. Souayah acknowledged that in 2012, the IOM determined that Pollard and Selby's case report represented CIDP rather than GBS. Additionally, Pollard and Selby failed to rule out other possible causes such as viral illness or provide anything other than a temporal relationship between the vaccine and onset of symptoms. Thus, in 2012, the IOM concluded only that there was insufficient evidence to accept or reject a causal relationship between tetanus-, diphtheria-, and/or pertussis- containing vaccines and either GBS or CIDP. Tr. 54-55, 123-24.[61]

Dr. Souayah also relied on his own research[62] on cases of GBS following Tdap vaccines reported to the United States' Vaccine Adverse Event Reporting System (VAERS). Pet. Ex. 14

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[56] The nodes of Ranvier are "constrictions occurring on myelinated nerve fibers at regular intervals of about 1 mm; at these sites the myelin sheath is absent and the axon is enclosed only by Schwann cell processes." *Dorland's* at 1281. Schwann cells are "any of the large nucleated cells whose cell membrane spirally enwraps the axons of myelinated peripheral neurons and is the source of myelin; a single Schwann cell supplies the myelin sheath between two nodes of Ranvier." *Dorland's* at 323.

[57] *See also* M.M. Dimachkie and R.J. Barohn (2013) [Pet. Ex. 14-Q] at 494; A.B. Pithadia & N. Kakadia [Pet. Ex. 14-NNN] at 221.

[58] This includes medical literature on other vaccines, including influenza, human papillomavirus (HPV), and hepatitis in association with GBS. *See* Pet. Ex. 14 at 13-19. As noted above, I have considered the entire record but have elected to discuss only the evidence relevant to resolution of this matter.

[59] J.D. Pollard & G. Selby, *Relapsing Allergic Neuritis*, 14 Clin. Exp. Neurol. 133 (1977) [Pet. Ex. 14-OOO]; J.D. Pollard & G. Selby, *Relapsing Neuropathy due to Tetanus Toxoid: Report of a Case*, 37 J. Neurol. Sci. 113 (1978) [Pet. Ex. 14-PPP] at 114.

[60] Institute of Medicine, *Adverse Effects Associated with Childhood Vaccines: Evidence Bearing on Causality* (1994) at 86-90 (addressing diphtheria and tetanus toxoids and GBS) [hereby filed as Ct. Ex. 3].

[61] Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* (2012) at 557-58 (addressing diptheria toxoids and GBS) [Resp. Ex. A-2]; *see also* Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* (2012) at 558-60 (addressing diphtheria toxoids and CIDP) [hereby filed as Ct. Ex. 4].

[62] N. Souayah et al., *Guillain-Barré syndrome after Vaccination in United States: A Report from the Centers for Disease Control and Prevention/ Food and Drug Administration Vaccine Adverse Events Reporting System*, 25 Vaccine 5253 (2007) [Pet. Ex. 14-JJJJ]; N. Souayah et al., *Guillain-Barré syndrome after Vaccination in the United States: Data from the Centers for Disease Control and Prevention/ Food and Drug Administration Vaccine Adverse Events Reporting System (1990 – 2005)*, 11 J. Clin. Neuromuscul. Dis. 1 (2009) [Pet. Ex. 14-KKKK].

at 20-21, Tr. 64. On cross-examination, Dr. Souayah acknowledged that VAERS is a passive reporting system which prevents confirmation of the individual's diagnosis, long-term course, and possible alternative causes. Additionally, VAERS data lacks an unvaccinated comparison group. Tr. 62-63, 123-26. Dr. Souayah also relied one case report of a patient diagnosed with GBS approximately one week after receiving a Tdap vaccine. Pet. Ex. 14 at 20.[63, 64]

Dr. Souayah agreed that "for [his] molecular mimicry theory to work, there has to be some kind of actual homology, *whether it's proven or not*." Tr. 64 (emphasis added). He agreed that "homology between… tetanus toxoid-containing vaccine and the human peripheral nervous system has not been shown in the literature." Tr. 65.

Dr. Souayah opined that molecular mimicry can cause small fiber neuropathy. Tr. 32. This opinion is supported by the 2011 article by Seneviratne and Gunasekara reporting cases of a GBS small fiber variant. They suggest that "small sensory fibers are a possible target for selective damage by autoantibodies" and recommending "immunological studies to identify the antibodies involved."[65] Similarly, in 2014, Makonahalli et al. suggested that their case report of a GBS small fiber variant includes "a distinct, as yet undiscovered, autoantibody involved in the pathogenesis that needs further studies" via "anti-ganglioside antibody testing."[66] Thus, molecular mimicry as a mechanism specifically causing small fiber neuropathy has been proposed, but not studied. Dr. Souayah recommended that such research include possible homology with tetanus, diphtheria, and pertussis.

Dr. Donofrio agreed that molecular mimicry is the leading explanation for GBS. Tr. 140. He submitted the Brighton group's article with diagnostic criteria for the four most common GBS variants, which provides: "Although host genetic or other phenotypic factors are likely to influence susceptibility to development of GBS in certain individuals, an association with specific HLA subtypes or immunogenetic susceptibility factors has not been consistently identified by existing studies." Resp. Ex. A-1 at 5.

Respondent's counsel asked: "For the purposes of the next few questions that the… special master finds that yes, indeed, petitioner had GBS of some form. What is your opinion as to whether the Tdap vaccine can cause GBS or a small fiber variant of GBS?" Tr. 122. Dr. Donofrio opined: "Well, first of all, I don't agree that the patient had GBS." *Id.* He went on to say that the Pollard & Selby case report of GBS/ CIDP following Tdap was not persuasive and that in general, case reports do not "even come close to proving causation." *Id.* at 123-24. Neither does VAERS data. *Id.* at 124-26. Dr. Donofrio opined that literature associating GBS

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[63] H. Ammar, *Guillain- Barré syndrome after Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine: A Case Report*, 502 J. Med. Case Rep. (2011) [Pet. Ex. 14-B].

[64] Dr. Souayah also referenced "a case report about a college student who developed GBS 4 days after Td vaccine." Pet. Ex. 14 at 19. However, he did not provide the full citation or file this case report. Thus, it is not included in my review of the literature concerning Tdap vaccine and GBS.

[65] Seneviratne and Gunasekara (2011) [Pet. Ex. 14-BBB] at 542.

[66] Makonahalli et al. (2014) [Pet. Ex. 14-AAA] at 151.

with other viruses and vaccines should not be extrapolated to Tdap vaccine. *Id.* at 126. He opined that it is not "generally accepted in the scientific community that Tdap vaccine can cause GBS via molecular mimicry." *Id.* at 126.

Dr. Donofrio agreed that small fiber neuropathy can be immune-mediated. Tr. 132-33. Small fiber neuropathy can be post-infectious "rarely," but he had yet to see a case. Tr. 133. He opined that "it's yet to be proven, that there is no convincing data, certainly, that shows that vaccines can cause a small fiber neuropathy, and certainly not Tdap." Tr. 140. Dr. Donofrio was not inclined to accept this theory until he was shown pathology and proper staining showing "antibody deposition on the small fibers, and those antibodies… cross-react[ing] to particles in the vaccination." Tr. 141. I asked whether this would involve "the actual biopsy material taken from the patient" with small fiber neuropathy. Tr. 147. Dr. Donofrio agreed. *Id.* I asked: "And how often is that done?" *Id.* Dr. Donofrio responded: "Oh, it isn't… it's not done." *Id.*

In this case, Dr. Donofrio submitted one report, testimony, the Brighton group and Asbury & Cornblath's diagnostic criteria for the most common forms of GBS, and the 2012 Institute of Medicine statement on Tdap and GBS. Dr. Donofrio did not submit any literature on small fiber neuropathy. This contrasts with previous cases in which respondent submitted evidence rebutting the petitioner's causation theory. *See* Resp. Post-Hearing Resp. at 30, citing *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1360-61 (Fed. Cir. 2013) (denying review of special master's denial of entitlement of flu-multiple sclerosis (MS) claim after respondent submitted studies showing that only certain portions of flu vaccine were cross-reactive with myelin basic protein which is damaged in MS, and respondent submitted studies that MS patients did not exhibit aggravated MS symptoms after flu vaccination);

Upon review, I agree that there are not significant verified case reports, population studies, and animal experiments supporting an association between Tdap vaccine and the most common GBS variants (AIDP, AMAN, AMSAN, and Miller-Fisher syndrome). *See, e.g.*, *Isaac v. Sec'y of Health & Human Servs.*, 108 Fed. Cl. 743 (2013) (denying review of special master's denial of entitlement where petitioner alleged that tetanus vaccine caused the most common GBS variant, AIDP, and respondent submitted the 2012 IOM study), *aff'd without opinion* 540 Fed. Appx. 999 (2013).

But importantly, the present case involves a GBS variant involving selective damage of the small fibers. Because of the difficulty obtaining objective evidence of small fiber damage and the other known explanations, immune-mediated small fiber neuropathy is likely to be overlooked. However, the limited case reports proposing a GBS small fiber variant invoke molecular mimicry and call for further research on the specific cross-reactivity involved. Dr. Souayah and Dr. Donofrio agreed that this research has not been conducted. Petitioner should not be faulted for the lack of published literature on point with his case. "[T]o require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Andreu*, 569 F.3d at 1379. Therefore, "a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Knudsen*, 35 F.3d at 549. *See also Salmins v. Sec'y of Health & Human Servs.*, No. 11-140V, 2014 WL 1569478 at *14 (Fed. Cl. Spec. Mstr. March 31, 2014) (accepting Dr. Souayah's opinion that HPV vaccine "can cause" GBS although there was no

published medical literature demonstrating homology); *Jones v. Sec'y of Health & Human Servs.*, No. 15-1239V, 2018 WL 7139212 at *14 (Dec. 21, 2018) (holding that the petitioner established that Tdap and/or other vaccines "can cause" small fiber neuropathy "while not yet borne out in the literature"); *LaPierre v. Sec'y of Health & Human Servs.*, No. 17-227V, 2019 WL 6490730, *20 (Fed. Cl. Spec. Mstr. Oct. 18, 2019) (finding that the evidence "barely preponderate[d]" in favor of a finding that Tdap vaccine can cause small fiber neuropathy under *Althen* prong one, but the petitioner in that case failed on *Althen* prong two).

I find that the weight of the evidence submitted in this case preponderates towards a finding that the Tdap vaccine can cause a small fiber GBS variant. Accordingly, petitioner has fulfilled *Althen* prong one.

C. *Althen* Prong Two: Logical Sequence of Cause and Effect

1. Legal Standard

To fulfill *Althen* prong two, petitioner must show, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F.3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148.

2. Discussion and Conclusion

As discussed above, I find that after receiving the Tdap vaccine on June 1, 2012, petitioner manifested the first symptoms of a small fiber neuropathy. His primary care provider and the first neurologist drew a causal association between these events. A lumbar puncture conducted 11 days after the vaccine did not reveal elevated CSF protein. However, that does not rule out an immune-mediated process. Petitioner's small fiber neuropathy was chronic and made more difficult to treat by his frustration with his medical providers and lack of diagnosis. The sequelae included cognitive problems, increased blood pressure, and other related physical manifestations. I find that the clinical course is logically connected and eventually explained by the objective findings of small fiber neuropathy with no other known cause in 2016. Petitioner has established *Althen* prong two.

D. *Althen* Prong Three: Medically Acceptable Temporal Relationship

1. Legal Standard

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the

phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 543 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

2. Discussion and Conclusion

Dr. Souayah opined that petitioner's onset of symptoms was approximately seven days after the Tdap vaccination, on or about June 8, 2012. Pet. Ex. 14 at 21; Tr. 33-37, 75. In Dr. Soauyah's opinion, the first symptoms were the "burning sensation, numbness, and change in taste." Tr. 37.[67] Dr. Souayah considered this to be an appropriate timeframe for his theory of molecular mimicry. In his report, he opined that this "corresponds to the time when the immune system starts producing antibodies against the vaccine." Pet. Ex. 14 at 21. At the entitlement hearing, he largely extrapolated from literature on the acceptable timeframe in which natural infection and vaccinations such as flu (but not Tdap) cause the most common GBS variants via molecular mimicry. Tr. 35-36.

Dr. Donofrio opined that the risk period for developing GBS is only documented in the literature after natural infection and for specific vaccines, such as influenza; there is no risk period for Tdap vaccination. Tr. 142.

There is limited information on the acceptable timeframe in which Tdap vaccine can cause a small fiber neuropathy through the mechanism of molecular mimicry. Dr. Souayah submitted literature on other foreign pathogens and other immune-mediated peripheral neuropathies. He also opined that the immune system starts to produce antibodies against the vaccine within seven to ten days. Dr. Donofrio did not opine why the timing with Tdap vaccine and small fiber neuropathy would be any different. Accordingly, I accept Dr. Souayah's opinion that the timing seen in this case is acceptable.

Additionally, the primary care provider and the first neurologist recorded that the temporal association supported vaccine causation, at least initially. *See, e.g.*, Pet. Ex. 2 at 63-64, 104-05. Moreover, two neurologists who saw petitioner later in his course and doubted that he had GBS or another peripheral neuropathy, still recognized the temporal association. Pet. Ex. 2 at 172-73; Pet. Ex. 16 at 166-77. Petitioner has established *Althen* prong three.

[67] Petitioner also reported "flu symptoms" around the same time, according to one email to Dr. Messner. Pet. Ex. 2 at 48. This is not mentioned anywhere else in the record. Dr. Souayah opined that these "flu symptoms", to the extent that they did occur, did not represent the onset of petitioner's symptoms. Tr. 38-39. Dr. Donofrio did not rebut this point. Based on the evidence submitted, I agree with Dr. Souayah.

E. Alternative Cause

1. Legal Standard

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d at 548; § 13(a)(1)(B). Respondent must demonstrate "[t]he factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux*, 717 F.3d at 1369. Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition."

2. Discussion and Conclusion

Before the entitlement hearing, respondent averred that petitioner had not satisfied his burden of proving a *prima facie* case of causation-in-fact; therefore, the burden had not shifted to respondent to prove by a preponderance of the evidence that some factor other than the Tdap vaccine was the actual cause of petitioner's condition. Resp. Pre-Hearing Brief at 24, *citing Bradley v. Sec'y of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993). Dr. Donofrio did not assert a specific alternative cause for petitioner's injury. *See generally* Resp. Ex. A; Tr. 80-150. Neither did respondent. *See generally* Resp. Post-Hearing Brief. Respondent has not established a specific alternative cause for the injury alleged in the petition.

V. Conclusion

For the reasons discussed above, I find that petitioner has established by a preponderance of the evidence that following the June 1, 2012 Tdap vaccine, he developed a small fiber neuropathy which constitutes a variant of GBS. Petitioner has also established *Althen* prongs one, two, and three. Respondent has not shown an alternative cause. Accordingly, petitioner is entitled to compensation. A separate damages order will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master