In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Date: June 12, 2023

HANS HOFER,	*	PUBLISHED
Petitioner,	*	No. 18-1752V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Ruling on Entitlement; Influenza ("Flu"); Brainstem Encephalitis; Monofocal; Nature of Injury; Autoimmune; Demyelination.
Respondent.	*	

Ronald Craig Homer & Meredith Daniels, Conway Homer, P.C., Boston, MA, for petitioner.
Julia Marter Collison, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

On November 12, 2018, Hans Hofer ("petitioner"), filed a petition for compensation under the National Vaccine Injury Compensation Program.[2] Petitioner alleged causation-in-fact between an influenza ("flu") vaccine which he received on December 15, 2015, and a central nervous system injury localized to his brainstem, which his treating providers diagnosed as encephalitis. Petition (ECF No. 1). Petitioner retained a medical expert who opined that the term "encephalitis" describes only *inflammation*, not a more specific nature or etiology thereof. Petitioner and his expert averred that the injury was likely autoimmune and demyelinating in nature with inflammation occurring in conjunction with the demyelination, which was caused in fact by the flu vaccine. Motion (ECF No. 55) at 1 and n. 2. Respondent, through his own medical expert,

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it to a publicly available website. This decision will appear at https://www.govinfo.gov/app/collection/uscourts/national/cofc or on the Court of Federal Claims website. **This means the decision will be available to anyone with access to the Internet.** Before the decision 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 decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[2] [2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

disputed Petitioner's explanation of injury as well as vaccine causation. For the reasons set forth in this opinion, I find that Petitioner is entitled to compensation.[3]

I. Procedural History

Petitioner timely filed his claim in November 2018. He also filed the medical records and affidavits required under the Vaccine Act designated as Exhibits ("Exs.") 1-18. In the fall of 2019, Respondent reported that he intended to defend the case. ECF Nos. 22, 24.[4, 5]

The parties were accordingly directed to file expert reports. In April 2020, petitioner filed an initial expert report from neurologist Carlo Tornatore, M.D..[6] Ex. 20. In August 2020, respondent filed a responsive report from neurologist Thomas P. Leist, M.D., Ph.D.[7] Ex. A.

[3] Pursuant to Section 300aa-13(a)(1), in order to reach my conclusion, I have considered the entire record including all of the medical records, statements, expert reports, and medical literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

[4] Respondent initially proposed to file his formal report pursuant to Vaccine Rule 4(c) setting forth his reasons for opposing compensation prior to the submission of any expert reports or other proceedings. ECF No. 22. Upon preliminary review of the case, recognition that it would involve a causation-in-fact analysis, and interest in expediting further proceedings, I directed Respondent to provide the more concise status report instead. ECF No. 23.

[5] Upon summarizing his tentative position towards the claim, Respondent also requested complete records of Petitioner's claim for social security disability insurance ("SSDI"). ECF No. 24. On January 16, 2020, Petitioner filed his SSDI file – which contains some updated medical records - as Ex. 19.

[6] Dr. Tornatore obtained an undergraduate degree in neurobiology from Cornell University in 1981; a master's of science degree from the Georgetown University Department of Physiology in 1982; and a medical degree from Georgetown University School of Medicine in June 1986. Ex. 21 at 2 (*curriculum vitae*). He completed an internship in internal medicine at Providence Hospital, followed by a residency in neurology at Georgetown University Hospital. *Id.* He was then hired at the National Institutes of Health ("NIH"), specifically at the National Institute of Neurological Disorders and Stroke ("NINDS"), where he worked in the laboratory of viral and molecular pathogenesis (researching "the interaction of viruses and the immune system") for three and one-half years, then served as section chief in the laboratory of molecular medicine and neuroscience for another three and one-half years. *Id.* at 2, 4; *see also* Ex. 20 at 2 (expert report). Dr. Tornatore has been employed at Georgetown University Medical Center as both an academic instructor and a clinician specializing in neurology since the 1990s – and has chaired the neurology departments at both the medical school and the hospital since 2015. Ex. 21 at 3. In his initial expert report, Dr. Tornatore stated that while his clinic primarily follows patients with multiple sclerosis ("MS"), they were also following 221 patients with acute disseminated encephalomyelitis ("ADEM" – a significant topic of discussion in this case); 115 patients with neuromyelitis optica ("NMO"); 373 patients with transverse myelitis ("TM"); 53 patients with central nervous system vasculitis; 113 patients with neuro-sarcoidosis; and 63 patients with various other inflammatory conditions of the brain and the spinal cord. Ex. 20 at 2. He is licensed to practice medicine in the District of Columbia, and he is board-certified in neurology. Ex. 21 at 2.

[7] Dr. Leist obtained an undergraduate degree from the University of Zurich in Switzerland in 1982; a Ph.D. in biochemistry from the same institution in 1985; and a medical degree from the University of Miami in Florida in 1993. Ex. B at 1. He interned in internal medicine at the University of Miami in Florida, and as a resident in neurology at Cornell Medical Center/ Memorial Sloan-Kettering Cancer Center in New York. *Id.* He then served as a senior clinical staff associate at NIH – NINDS for three years. *Id.* Dr. Leist has been a member of the Society of Neuroimmunology since 1996. *Id.* at 2. He began teaching neurology at Thomas Jefferson University in 2000, where he was named as a full professor in 2014. *Id.* He is also a clinician at the university's hospital, and the director of clinical neuroimmunology at its MS center since 2000. *Id.* He stated that he was "regularly involved in the care of patients with neuro-immunological conditions including [MS], transverse myelitis, [NMO], [NMO] syndrome, and immune

Respondent simultaneously filed his report pursuant to Vaccine Rule 4(c). Respondent's Report ("Resp. Rep't") at ECF No. 24.

At an October 2020 status conference, I reviewed the initial expert reports and raised additional questions. ECF No. 40. In January 2021, petitioner filed Dr. Tornatore's supplemental report. Ex. 27. In February 2021, respondent filed Dr. Leist's second report. Ex. C.

In March 2021, at a status conference held pursuant to Vaccine Rule 5, I communicated that both parties carried litigative risk and should pursue informal resolution – while in the alternative, permitting them to seek either a ruling on the record as it stood or a hearing on entitlement. ECF No. 46. In May 2021, petitioner conveyed a settlement demand to respondent and the parties confirmed their openness to either method of formal adjudication if that proved to be necessary. ECF No. 47. In July 2021, respondent reported that he was not open to informal resolution. ECF No. 51. After discussion with counsel, I determined not to hold an entitlement hearing based on my review of the record and both parties' aforementioned consent. ECF No. 53.

In October 2021, petitioner filed a Motion for a Ruling on the Record ("Motion"), at ECF No. 55. In December 2021, respondent filed his Response, at ECF No. 56. Petitioner promptly filed a Reply, at ECF No. 57. The matter is now ripe for adjudication.

II. General Legal Standard

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

Petitioner's burden of proof is by a preponderance of the evidence. Section 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, the petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *see also Pafford v. Sec'y of Health & Hum. Servs.,* 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is due to "factors unrelated to the administration of the vaccine." Section 13(a)(1)(B).

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disorders of the peripheral nervous system." Ex. A at 1. He is licensed to practice medicine in Pennsylvania, Maryland, and New York (inactive) and is board-certified in neurology. Ex. B at 1. However, Dr. Leist described his own specialty as "neuroimmunology." Ex. A at 1.

To receive compensation through the Program, petitioner must prove either (1) that she suffered a "Table Injury"— i.e., an injury listed on the Vaccine Injury Table— corresponding to a vaccine that she received, or (2) that he suffered an injury that was actually caused by a vaccination. See Sections 11(c)(1), 13(a)(1)(A); *Capizzano v. Sec'y of Health & Hum. Servs.,* 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Where as here, the petitioner does not allege a Table Injury, the petitioner must prove that the vaccine received actually caused the injury. To do so, the petitioner must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and the injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for the injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and the injury ("*Althen* Prong Three"). Section 13(a)(1); *Althen*, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Recently, in *Kottenstette*, the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[]" *Kottenstette v. Sec'y of Health & Hum. Servs.*, 861 Fed. Appx. 433, 441 (Fed. Cir. 2021) (citing *Knudsen*, 35 F.3d at 549). Causation "can be found in vaccine cases…. without detailed medical and scientific exposition of the biological mechanisms." *Knudsen*, 35 F.3d at 549. It is not necessary for a petitioner to point to conclusive evidence in the medical literature linking the vaccine to the injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1325 (Fed. Cir. 2010).

The petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. Section 13(a)(1). In determining whether the petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." Section 13(b)(1)(A).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, the *Daubert* analysis has been used in the weighing of the scientific evidence actually proffered and heard, rather than as a tool for the pre-trial exclusion of expert testimony. *Davis v. Sec'y of Health & Hum. Servs*., 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g., Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

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 & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Summary of Relevant Facts[8]

A. Prior Medical History and December 15, 2015, Vaccination

At the time that petitioner received the subject flu vaccine, he was 58 years old. He was an active employee and part owner of a land surveying business in Indiana. Ex. 12 at ¶ 1. He sought medical care infrequently. His medical history included an episode of Bell's palsy in February 2009; chronic neck and low back pain; insomnia; and obstructive sleep apnea for which he began using a CPAP machine in 2013. *See generally* Exs. 2-3. He also had a 39-year history of tobacco use and smoked approximately one pack per day. Ex. 3 at 34. He received a previous flu vaccine on October 30, 2014, without any recorded adverse events. Ex. 6 at 2.

Petitioner received the subject vaccine during a one-year follow-up appointment for his apnea, at Parkview Physicians Group ("PPG") – Sleep Medicine, with the nurse practitioner ("NP") Karin L. Mohs. Ex. 1 at 1; Ex. 3 at 33-42. On the subjective review of systems, petitioner reported post-nasal drip but no cough, shortness of breath, or headache. Ex. 3 at 40. On physical exam, the NP observed no oropharyngeal exudate, wheezes or rales, or any other symptoms that would be consistent with sinusitis or an upper respiratory infection. *Id.* Nevertheless, the NP recommended nasal saline and over-the-counter Flonase for petitioner's report of "some nasal congestion." *Id.* at 41. It is not clear from the note whether the NP was merely recommending a

[8] I have reviewed both parties' expert reports and briefing in order to identify the key factual issues bearing on entitlement. These are sufficiently addressed in the medical records. I have also reviewed petitioner's affidavit (Ex. 12), which is generally consistent with and does not diverge from the medical records on any key issues bearing on entitlement. Therefore, the affidavit is generally not cited.

common over-the-counter remedy for periodic nasal congestion or if petitioner had congestion currently at the time of this encounter.

B. January 9, 2016: Urgent Care Encounter

Twenty-five (25) days after the flu vaccination, Petitioner presented to an urgent care facility, where Shawn Kidder, M.D., recorded: "Complains of nausea began at 6PM last night, vomiting at 7PM, very dizzy – balance is very off. Dull, nagging headache since Christmas – pain at top and back of scalp." Ex. 4 at 2. The review of systems was negative for congestion, sore throat, headache, cough, or shortness of breath. *Id.* Physical exam of the nose was "normal." *Id.* at 4. Dr. Kidder assessed 1) non-intractable episodic headache – unspecified headache type and 2) subacute maxillary sinusitis. *Id.* at 5. Dr. Kidder recommended lab work. *Id.* at 6. He prescribed both the antibiotic Keflex (cephalexin) and the antihistamine Antivert (meclizine) which is used to treat motion sickness and dizziness.

C. January 10 – 20, 2016: Parkview Regional Medical Center ("PRMC") Hospitalization[9]

The next day, January 10, 2016, Petitioner presented to the Parkview Regional Medical Center emergency room with a one to two-week history of headache particularly in the posterior occipital region; a two-day history of dizziness and vomiting; and worsened right-sided facial droop since that morning (about which petitioner stated: "I have had Bell's palsy in 2009 but it's worse today"). Ex. 6 at 72-79. The problem list and the history reflect petitioner's cigarette-smoking. *Id.* at 74, 76. A brain MRI with and without contrast was ordered "to exclude possibility of stroke." *Id.* at 79. Radiologist Peter J. Mehta, M.D., recorded:

> *Discussion: …*There is no evidence of pathologic diffusion restriction. [A]bnormal T2/FLAIR hyperintensity involving the inferior aspect of the left pontine tegmentum and extensively involving the amygdala, with involvement of the entire left half of the medulla and the bilateral medullary periods. There is relative sparing of the right posterior medulla. This area shows abnormal, amorphous enhancement…There is no evidence of internal hemorrhage within the lesion.
>
> *Impression:* Findings compatible with a subacute ischemic infarct involving the medulla as described, in the territory of the posterior inferior cerebellar arteries. The appearance of this lesion suggests infarct occurring at least 7 days ago. Follow up brain MRI in 4-6 weeks is recommended to rule out the unlikely possibility of an underlying neoplasm. Markedly diminutive vertebral and basilar arterial flow voids. Consider CT angiogram of the head and neck for further evaluation.

Ex. 6 at 334-35; *see also id.* at 79-81 (admission note). A CT angiogram was performed on the same day showing patent cervical and intracranial vasculature. *Id.* at 78. The CT found, "No

[9] Of note, the problem list carries over previous notations from within the Parkview health system – including the PPG Sleep Medicine NP's December 15, 2015, notations of "need for influenza vaccination; insomnia with sleep apnea; nasal congestion." *Compare* Ex. 3 at 32-33; Ex. 6 at 2.

evidence of high grade cervical or proximal intracranial arterial stenosis, occlusion, filling defect or aneurysm. Normal variant anatomy with persistent fetal circulation and diminutive calibre of the distal vertebral and basilar arteries." *Id.* 335.

Following admission, petitioner was evaluated by neurologist Roger C. Gietzen, M.D., who primarily suspected an ischemic stroke but noted that the MRI findings were somewhat abnormal for such an injury. *Id.* at 199. Dr. Gietzen's differential diagnosis also included "neoplasm, infection, demyelination, or inflammation." *Id.* He also specifically considered multiple sclerosis although Petitioner "was older than the typical age of onset." *Id.* Dr. Gietzen recommended a lumbar puncture to facilitate "testing for cytology, MS panel, and inflammatory or infectious causes." *Id.*

On January 11, 2016, neurologist Madhav Bhat, M.D., reviewed the imaging done to date and assessed that Petitioner's condition was most likely secondary to an acute brainstem infarction rather than "tumor or demyelination." Ex. 6 at 87-94. He ordered the testing previously suggested by Dr. Gietzen. Cerebrospinal fluid analysis ("CSF") revealed elevated white blood cells (13) red blood cells (16), protein (110), and IgG (6.9) Ex. 6 at 293-94, 304-05. An MS profile was "abnormal" for elevations in the CNS IgG synthetization rate, albumin index, IgM, and IgA. *Id.* at 310-11. There were no oligoclonal bands. *Id.* at 310.

On January 13, 2016, the radiologist Dr. Mehta amended his initial report, based on a review of the medical record and "correlation with the CSF results," and wrote that the "previously described findings should also be considered with revised differential diagnosis including brainstem encephalitis, a demyelinating disease such as ADEM or neuromyelitis optica [NMO], evolving subacute ischemic infarct, or a brainstem glioma." Ex. 6 at 334, 1005. However, the MRI "did not show evidence of optic nerve edema to suggest acute optic neuritis." *Id.*

Dr. Bhat recorded: "Need to rule out demyelination/ADEM/NMO or paraneoplastic disease… Need repeat brain MRI with contrast, MRI cervical spine with contrast, and NMO antibody." Ex. 6 at 120.

On January 13, 2016, a second MRI of the brain revealed: "Relatively unchanged inflammatory changes involving brain stem. Encephalitis or demyelination are suspected. Longer-term follow-up is recommended to assess stability and to exclude brainstem glioma." Ex. 6 at 338; *see also id.* at 116, 133 (neurologists Drs. Bhat and Curfman's plan for continuation of aspirin and clinical monitoring).

Petitioner developed worsening dysphagia (difficulty swallowing) and ataxia (with difficulty speaking). *See* Ex. 6 at 116, 122. He failed a swallow study and was provided with a nasogastric ("NG") feeding tube. Ex. 6 at 127.

On January 15, 2016, neurologist James C. Stevens, M.D., conducted an evaluation – but his dictated notes were not recorded. Ex. 6 at 140. A nurse summarized: "Dr. Stevens did order IV Solumedrol [steroids] for the patient and entered an ENT consult for right maxillary sinusitis. Dr. Stevens also reiterated that patient did not have a stroke, but instead an inflammation of the medulla." *Id.* at 144.

Ear, nose, and throat ("ENT") specialist Douglas A. Nuckols, M.D., then consulted on the case, noting the visualized "cysts in sinus and sinusitis." Ex. 6 at 202. "[Petitioner] had at least 2 year [history] of congestion and rhinorrhea/pnd ("post nasal drip") which is worse in the morning. Has not had any treatment for this to date, just blows his nose several times per day… Symptoms are year-round." *Id.* On January 16, 2016, Dr. Nuckols assessed:

> Chronic sinusitis/ left maxillary mucus retention cyst with left deviated septum. Findings chronic and present at similar degree from CT in 2010.[10] *Unrelated to current symptoms* but should be addressed. Would recommend Omnicef 300 bid (or similar) for 28 days. Could also benefit from Flonase daily once NG tube is out. Should follow up with me in the office in 4 weeks. Likely will repeat CT sinus at that point to see if inflammation is clearing.

Ex. 6 at 206 (emphasis added). This ENT consultation is reflected in the subsequent Parkview medical records, and therefore presumably incorporated in the opinions of Parkview neurologists and other treaters.

On January 16, 2016, internal medicine physician Suresh K. Ravuri, M.D., recorded that Petitioner had "inflammation of brain stem and no specific cause was found." Ex. 6 at 144.

Additionally, neurologist Ajay S. Gupta, M.D., characterized Petitioner's injury as "brainstem encephalitis." Ex. 6 at 149. Dr. Gupta recorded: "CSF MS profile is negative. Paraneoplastic panel is negative (anti-HU antibody, anti-RI antibody, anti-Yo antibody)." *Id.* at 153. Dr. Gupta ordered CSF testing for "epilepsy autoimmune" antibodies. *Id.* at 154.[11] On January 17th, Dr. Gupta recorded that petitioner was concerned about Lyme disease because his business partner had recently contracted the disease and Petitioner himself spent a lot of time in the woods. Ex. 6 at 158. Therefore, Dr. Gupta ordered testing for antibodies against Lyme disease. *Id.* at 163.[12] But based on the available information, Dr. Gupta's impression remained "brain stem encephalitis

[10] This 2010 CT scan's report has not been filed.

[11] The epilepsy autoimmune evaluation was both ordered by Dr. Gupta and collected at Parkview on January 16, 2016. Ex. 6 at 920. However, the actual testing was analyzed offsite (at the Mayo Clinic) and not printed until January 27, 2016. *Id.* From a review of the records and the parties' briefing, it is not clear whether any Parkview neurologists or other treaters evaluated the results. *See generally* Exs. 6, 7. The testing was negative for the following antibody types: NMDA-R; neuronal (V-G) N+ channel; GAD65; GABA-B-R; AMPA-R; anti-neuronal nuclear types 1-3; anti-glial nuclear type 1; Purkinje cell cytoplasmic types 1-2 and Tr; Amphiphysin; N-type calcium channel; and ACB receptor (muscle) binding; CRMP-5-IgG. *Id.*

The epilepsy autoimmune evaluation's only positive finding was for P/Q type calcium channel antibodies at 0.06 nmol/L (elevated above the reference range of ≤ 0.02 nmol/L). Ex. 6 at 920. The report provides: "This profile, in the proper clinical context, would support neurological autoimmunity. The influence of monoclonal and polyclonal gammopathies is uncertain. Oncological significance is uncertain." *Id.*

[12] Like the epilepsy autoimmune testing, it is not clear whether any Parkview neurologists or other treaters evaluated the results of the Lyme testing. However, at subsequent consultations at the Cleveland Clinic, the Lyme testing was noted to be negative. *See, e.g.*, Ex. 5 at 5, 33.

of unknown etiology." Ex. 6 at 163; *see also id.* at 164 (neurologist Dr. Bhat concurring the following day).

On January 18, 2016, a cytology specimen was analyzed. *See* Ex. 6 at 323-24, 329-330. The cytology report found "only rare non-specific inflammatory cells and red blood cells." *Id.* at 330. The "diagnosis" field was left blank. *Id.*

On January 19, 2016, petitioner underwent insertion of a percutaneous endoscopic gastrostomy ("PEG") feeding tube. Ex. 6 at 179, 222-23. That same day, Dr. Gupta summarized that petitioner's condition had not improved with Solumedrol. *Id.* at 178. Thus, he was started on a five-day course of intravenous immunoglobulin ("IVIg"). *Id.* If that delivered no response, another option would be plasmapheresis. Ex. 6 at 178. Dr. Gupta authorized transfer to Parkview's inpatient rehabilitation hospital the following day. Ex. 6 at 188-95, 229-235.

D. January 20 – February 2, 2016: Parkview Hospital Randallia Inpatient Rehabilitation

Following petitioner's transfer to Parkview inpatient rehab, the same neurology team monitored petitioner and maintained the assessment of brainstem encephalitis of unknown etiology. Ex. 6 at 1055-58; Ex. 7 at 136-38. As of January 22, 2016, petitioner was not displaying any "new or worse symptoms" or any improvement. Ex. 6 at 972-74. But by January 25, 2016, upon completion of IVIg, petitioner reported improved right-sided vision. *Id.* at 983. His family perceived that his face was more symmetric and that his voice was clearer. *Id.* However, he continued to receive nutrition through a PEG tube and participated in physical, occupational, and speech therapies. *See generally* Ex. 7. His course was also complicated by pneumonia. Ex. 6 at 1026, 1058-61.

During the rehabilitation course, Dr. Gupta recorded that a Dr. Dozier[13] had recommended evaluating petitioner's injury via craniotomy and open biopsy. Ex. 6 at 976. Indiana University Medical Center ("IUMC")'s neurosurgery team was consulted. *Id.* However, the Parkview neurology team decided to defer the biopsy in favor of follow-up imaging. *See id.* at 995.

On February 1, 2016, a third brain MRI visualized: "T2 and FLAIR signal abnormality within the brainstem; appears unchanged from prior examination with patchy, predominantly peripheral enhancement within the left aspect of the medulla is concerning for an underlying mass. The differential would still include demyelinating process, less likely subacute infarct given the appearance of the enhancement in relationship to the T2 and FLAIR signal abnormality." Ex. 6 at 1106-07.

On February 2, 2016, Petitioner was discharged from inpatient rehabilitation. Ex. 6 at 1058-61. He would continue physical, occupational, and speech therapies on an outpatient basis. *Id.* at 1061. The Parkview neurology team was continuing to "discuss diagnosis and possible referral to IUMC." *Id.* He was instructed to follow-up with Dr. Gupta in four weeks. *Id.*

[13] From internet research, this reference appears to be to James Dozier, M.D., a neurosurgeon affiliated with Parkview. *See* https://www.parkview.com/find-a-doctor-profile/288/james-dozier (last accessed October 26, 2022).

E. February 2016 – 2019: Subsequent Course Including Cleveland Clinic, Parkview Neurology, and ENT Follow-Ups

On February 17, 2016, Petitioner presented for a second opinion at the Cleveland Clinic. *See generally* Ex. 5.[14] Neurologist Jeremy Rich, M.D., reviewed the prior medical records and recorded petitioner's history, including that he had smoked one pack of cigarettes per day up to January 2016. *Id.* at 1-5. Dr. Rich summarized: "[P]resented in January 2016 with acute onset of nausea and vomiting, gait imbalance, and diplopia. MRI showed brainstem abnormality. Work up for infectious, demyelinating, and paraneoplastic syndrome negative. Minimal response to IVIg and steroids. Repeat MRI unchanged but concerning for underlying mass." *Id.* at 5. Dr. Rich's assessment was a "brainstem lesion of unknown etiology." *Id.*

Neurosurgeon Alireza Mohammadi, M.D., also consulted on the case. Ex. 5 at 10-21. Dr. Mohammadi recorded: "It's very hard to tell if this is a tumor versus inflammation/infection versus demyelinating disease. He had extensive work up with mild elevation in WBC and protein of CSF. Still, we need to do some additional work up for rare infectious disease problems based upon his work history and recent sinusitis." *Id.* at 13. Drs. Mohammadi and Rich also agreed that "given the high risk of biopsy in this location and also improvement in clinical status," they would order a repeat MRI. *Id.* If the MRI was worse, correlated with petitioner's clinical symptoms, and no other work up is positive, the next step would be a brain biopsy. *Id.*

Shortly thereafter, from February 21 – 25, 2016, petitioner was hospitalized for pneumonia. Ex. 6 at 1733-38 (discharge summary).

On March 3, 2016, a fourth MRI of petitioner's brain visualized a "significantly improved T2 and FLAIR signal abnormality within the left aspect of the medulla favored to represent resolving encephalitis with mild peripheral enhancement along its left lateral margin." Ex. 2 at 28.

Upon petitioner's return to the Cleveland Clinic on March 9, 2016, neurosurgeon Dr. Mohammadi recorded: "Neurologically and radiologically improved. There is no reason for brain biopsy at this point… I will see him if biopsy is needed[.]" Ex. 5 at 23; *see also id.* at 27-29 (neurologist Dr. Rich's progress note).

The following day, infectious disease specialist Adarsh Bhimraj, M.D., consulted on the case and summarized that petitioner was "clinically and radiologically improving. It could be from the treatments he received (steroids, IVIg, or the antimicrobials) or he is improving by himself." Ex. 6 at 36. Dr. Bhimraj wrote that the "work up done was largely unremarkable" and he did not note any specific findings to be relevant to the understanding of the injury. *Id.* at 33.

Dr. Bhimraj listed some potential etiologies including Bickerstaff's brainstem encephalitis. *Id.* He noted that "a workup in encephalitis might be negative, and given that he is clinically improving, would avoid an invasive work up like repeating an LP for CSF analysis. But if he worsens or if any of the current tests warrant further testing, we will consider that." *Id.* at 37. Dr.

[14] *See also* Ex. 2 at 26 (February 12, 2016, primary care notation that Petitioner and his wife initially "thought they were going to be referred to a tertiary care center" – presumably, IUMC – and then determined to go to the Cleveland Clinic).

Bhimraj ordered additional testing including for syphilis IgG; HIV; and antibodies for hepatitis C, West Nile Virus, and CRP – all of which were negative. *Id.* at 37-47. GQ1B antibody was "inconclusive." *Id.* at 42.

At a March 7, 2016, appointment, the ENT specialist Dr. Nuckols, decided "to evaluate max[illary] sinus? longstanding cyst vs. infection." Ex. 9 at 74. Thus on March 18th, petitioner underwent a repeat CT scan. *Id.* at 68. On April 8th, Dr. Nuckols recorded that the repeat CT scan showed "no evidence of sig[nificant] sinusitis that would benefit from further t[reatment]." *Id.*at 55. Dr. Nuckols did not plan any further treatment or follow-up appointments. *Id.*[15]

At a May 26, 2016, follow-up appointment at the Parkview outpatient neurology practice, petitioner was noted to be frustrated and searching for "answers as to the specific type of encephalitis; want more testing + treatment." Ex. 8 at 12. However, Dr. Gupta did not offer any further testing or recommendations. *Id.* at 13.

On June 14, 2016, a fifth MRI of the brain found: "What appeared originally to be a diffuse long T2 enhancing process involving the medulla to the left of midline and the pons compatible with encephalitis or infarct, has now nearly entirely resolved with no enhancement, no mass, and only tiny residual focus of long T2 gliosis in the left pontomedullary junction." Ex. 8 at 10-11.

On June 14, 2016, petitioner returned to the Cleveland Clinic for the final time. Ex. 5 at 48-56. The neurologist Dr. Rich recorded that while the repeat MRI was significantly improved, petitioner's clinical improvement had been slow, and he remained quite symptomatic. *Id.* at 50. He would continue with serial MRI scans and therapy. *Id.* The assessment remained "brainstem lesion of unknown etiology," not representing a tumor. *Id.*

On July 27, 2016, petitioner followed up with the Parkview neurologist Dr. Gupta. Ex. 8 at 2. Dr. Gupta noted that the patient had improved ambulation, speech and swallowing. *Id.* Further, Dr. Gupta noted that petitioner was undergoing intense speech therapy and was trying a dental soft diet but still on PEG tube at home. *Id.* Petitioner also reported that oral secretions had decreased markedly but he continued to have loss of sensation on the right side. *Id.* Dr. Gupta's impression was: "Encephalitis. Markedly improved. It is unknown if patient had brainstem encephalitis or a non-specific episode of brainstem demyelination which may have been filed early mediated following influenza vaccination a few months earlier…" *Id.* at 4.

Subsequent medical records document ongoing residual effects – including use of the PEG feeding tube until December 2016. *See* Ex. 9. Petitioner did not have further neurology follow ups.

At a February 2017 primary care consult, petitioner questioned whether a nares cyst was causing his "constant sinus drainage." Ex. 2 at 62. He reported no change in symptoms despite using Flonase since it was prescribed by the ENT specialist Dr. Nuckols in January 2016. *Id.* The primary care physician did not offer any assessment or plan for this complaint. *Id.* at 62-63.

[15] In advance of the April 21, 2016, appointment, petitioner contacted the ENT office to raise "whether symptoms may have been triggered following a flu vaccination he had in 12/2015. Specifically… whether he has Bickerstaff's brainstem encephalitis." Ex. 9 at 56-57. Dr. Nuckols's encounter record does not address this question.

In June 2019, upon the primary care physician's recommendation, the Parkview neurologist Dr. Curfman conducted "a routine neurologic follow-up" for petitioner's "chronic balance and swallowing difficulties status post brainstem encephalitis" in January 2016. Ex. 19 at 823-28.[16] In the history section, Dr. Curfman wrote that "MRI showed demyelinating changes in the lateral medulla and pontomedullary region without any signs of ischemia." *Id.* Additionally: "CSF analysis revealed elevated protein to 110 with elevated WBC to 13. It was speculated this may have been triggered by a vaccination he had received several weeks earlier." *Id.* Dr. Curfman assessed that as of June 2019, petitioner had "ataxia and dysphagia as a late effect of left pontomedullary inflammation from a post-vaccination encephalitis." *Id.* at 828. He recommended a routine follow up in one year. *Id.*

The Social Security Administration ("SSA") denied petitioner's initial disability benefits claim in August 2019. Ex. 19 at 875-78. Petitioner filed his SSA records in January 2020. *See generally* Ex. 19. He avers that SSA ultimately granted the claim in 2021. Motion at 24-25. However, no further SSA or medical records have been filed.

IV. Analysis

A. Nature of Injury

1. Introduction and Legal Standard

The Federal Circuit established the test for actual causation of an off-Table injury in *Althen*, 418 F.3d at 1278. In that case: "There was no dispute as to whether the petitioner, Margaret Althen, actually suffered from a central nervous system demyelinating disorder. Therefore, the Federal Circuit was not presented with a case in which the diagnosis itself was questioned, but one in which causation of the injury by the vaccine was the issue in dispute." *Doe v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 597, 611 (2010) (citing *Althen*, 418 F.3d at 1282), *aff'd, Lombardi v. Sec'y of Health & Hum. Servs.*, 656 F.3d 1343 (Fed. Cir. 2011).

Special masters are generally not tasked with diagnosing injuries. In *Lombardi*, the Federal Circuit explained: "The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the petitioner's injury.'" *Lombardi*, 656 F.3d at 1343, *citing Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1382 (Fed. Cir. 2009).

However, the Federal Circuit has determined that in certain instances, "if there is a dispute as to the nature of a petitioner's injury, the special master may opine on the nature of the petitioner's injury." *Contreras v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1363, 1368 (Fed. Cir.

[16] Although the record characterizes petitioner as a "new patient," it also notes that petitioner's history was "well-documented." Ex. 19 at 823. Moreover, Dr. Curfman was on the original neurology team in January – February 2017. *See, e.g.*, Ex. 6 at 133-37, 981-84, 993-996, 1006-09 (selected hospital records); Ex. 7 at 136-38 (inpatient rehab admission note).

2017), *citing Hibbard v. Sec'y of Health & Hum. Servs.*, 698 F.3d 1355 (Fed. Cir. 2012); *see also Locane v. Sec'y of Health & Hum. Servs.*, 686 F.3d 1375 (Fed. Cir. 2012); *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339 (Fed. Cir. 2010)).

In *Hibbard*, the Federal Circuit reasoned: "If a special master can determine that a petitioner did not suffer the injury that she claims was caused by the vaccine, there is no reason why the special master should be required to undertake and answer the separate (and frequently more difficult) question whether there is a medical theory, supported by 'reputable medical or scientific explanation,' by which a vaccine can cause the kind of injury that the petitioner claims to have suffered." 698 F.3d at 1365.

While the special master is not required to reach a specific diagnosis, the special master may appropriately evaluate at least the nature of petitioner's injury and whether that aligns with petitioner's theory. For example, in *Broekelschen*, the petitioner posited "transverse myelitis [which] is an inflammatory event caused by an immune response," while the respondent posited "anterior spinal artery syndrome, [which] is a vascular event caused by a blockage." 618 F.3d at 1346. The Federal Circuit observed: "Nearly all of the evidence on causation was dependent on the diagnosis" and because the injury itself [was] in dispute, the proposed injuries differ[ed] significantly in their pathology, and the question of causation turn[ed] on which injury [the petitioner] suffered." *Id.* Accordingly, the Federal Circuit held "it was appropriate… for the special master to first determine which injury was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury." *Id.*

In contrast, in *Contreras*, the Court of Federal Claims held that the special master erred by diagnosing the petitioner's illness – as TM and not Guillain-Barré syndrome ("GBS") – before evaluating the *Althen* prongs. 107 Fed. Cl. 280, 292-93. The Court reasoned that the case contained "ample evidence that TM and GBS are similar diseases with similar pathologies" and the parties' "unified position [was] that an exact diagnosis of [the petitioner's illness] was not required to rule on causation." *Id.* at 293. The Court of Federal Claims articulated that "the general rule is that the special master should not conduct a differential diagnosis, at the outset of the causation analysis, to choose one diagnosis over another, or over a combination of diagnoses." *Id.*, *aff'd* 844 F.3d 1363; *see also Andreu*, 569 F.3d 1367, 1378 (holding that the special master need not determine whether an initial seizure was febrile or afebrile for purposes of assessing vaccine causation).

Relevant to this inquiry, the Vaccine Act provides that a special master must consider the record as a whole including any medical diagnosis contained therein. Section 300aa-13(b)(1). However, no diagnosis in the medical records is "binding on the special master." *Id.* Rather, "[i]n evaluating the weight to be afforded to any such diagnosis… the special master… shall consider the entire record and the course of the injury, disability, illness, or condition until the date of the judgment of the special master." *Id.* The special master shall also consider any expert opinions and additional medical scientific evidence in the record. *Id.*

Here, it is undisputed that Mr. Hofer's injury was acute, monophasic, and restricted to the brainstem. The treating providers narrowed their initial differential diagnosis by ruling out a stroke or other vascular event, and eventually eliminating a neoplasm or underlying mass when the MRI

scans showed resolution of the T2 hyperintensities.[17] The treating providers best characterized this injury as encephalitis recognizing that the encephalitis could have been a demyelinating event. Petitioner, through his expert Dr. Tornatore, argued that the more specific nature of injury was autoimmune demyelination. Exs. 20, 27; Brief at 31; Reply at 2.

Respondent argued that petitioner "ha[d] not demonstrated preponderant evidence" of autoimmune demyelination. Response at 7. Respondent maintained that encephalitis is an acute inflammatory process with "many possible etiologies." *Id.* at 7-8. His expert Dr. Leist opined that encephalitis is "usually caused by a viral or bacterial infection ***or*** by the immune system attacking brain tissue." Ex. A at 7 (emphasis added); accord Ex. 27 at 6.

Respondent contended that petitioner's encephalitis was more likely caused by unspecified pathogens associated with his history of smoking and chronic sinusitis. ECF No. 24 at 1-2. However, Dr. Leist's opinion as to this alternative cause is quite brief. He did not point to an infectious etiology as opposed to an autoimmune one while recognizing that encephalitis could be caused either by infection or by an immune system attack on the myelin. He did not address the fact that the petitioner's sinus/nasal symptoms were low grade and had not changed in years with a CT done in 2010 showing the same condition of the sinuses as the one done at Parkview. Ex. A at 7; *see also* Ex. C at 4.

Thus, it is less clear that the nature of injury *must* be evaluated prior to the *Althen* prongs. The parties' briefing does not address this point or cite to any case law such as *Broekelschen* and *Contreras*. *See* Respondent's Report at 2-6; Motion at 25-28, 31-37; Response at 6-9; Reply at 2-5. Nevertheless, I will review this issue first, consistent with the parties' framing.

2. Treating Providers

Respondent argued that no treating providers "determined that petitioner suffered from a demyelinating condition," primarily because they "*rejected* ADEM." Response at 8 (citing *id.* at 4; Ex. A at 6). But as further discussed below, the "D" in ADEM stands for dissemination. The lesions in Mr. Hofer's brain were localized to the brainstem and were not disseminated. The term ADEM does not encompass all CNS demyelinating injuries and alternative demyelinating conditions were not ruled out by the treating providers because they recognized that the lesions were not disseminated. Furthermore, a demyelinating condition was found to be one of the two remaining diagnoses on the differential through the end of his treatment.

The Parkview providers (including neurologists Drs. Gietzen, Bhat, Curfman, Stevens, and Gupta) and Cleveland Clinic providers (including neurologists Drs. Rich and Mohammadi) consistently characterized the injury as a brainstem *encephalitis*. Encephalitis describes an acute *inflammatory* process without any further specificity. The inflammation can be caused by direct viral or bacterial infection or by an autoimmune demyelinating response. Here, Mr. Hofer's treating providers continued to consider autoimmune demyelination as one of two most likely explanations of petitioner's brainstem encephalitis. The treating providers could not ultimately

[17] A vascular event would include an occlusion or blockage reducing blood flow, thereby disrupting neurological activity. *Broekelschen*, 618 F.3d at 1342.

confirm the specific nature of the injury without a brain biopsy, which carried significant risk that was not justified in light of petitioner's clinical improvement at the time that a biopsy was being considered. Ex. 5 at 13, 23 (explanation by Cleveland Clinic neurosurgeon Dr. Mohammadi). Thus, the parties' experts were left to offer their own, differing opinions regarding petitioner's diagnosis that was narrowed to demyelination or just undifferentiated encephalitis.

3. MRIs

The experts reviewed both the medical records and the images from petitioner's repeat brain MRIs. After review, Dr. Tornatore diagnosed petitioner with "focal inflammatory changes in the medulla consistent with inflammatory brainstem demyelination." Ex. 27 at 6. He observed the "remarkable improvement in the inflammation" between January 10, 2016, and June 14, 2016 MRIs and stated that the improvement "is very typical for a demyelinating inflammatory process such as ADEM or MAID,"[18]based on his three decades of clinical experience. *Id.* at 6-7.

The initial impression of petitioner's MRI by the radiologist was that the "findings were compatible with a subacute ischemic infarct involving the medulla." Ex. 6 at 334. However, an addendum was added, which provides, "Upon further review of the medical record and correlation with cerebral spinal fluid results, alternative etiologies of the previously described findings should also be considered, with revised differential diagnosis including brainstem encephalitis, a demyelinating disease, such as ADEM or neuromyelitis optica." *Id.* With petitioner's rapidly progressing symptoms of diplopia, dysphasia and ataxia, along with elevated protein in the CSF and CSF pleocytosis, neurologist Dr. Gupta wrote that "brain stem ischemia was considered less likely," and that "A possibility of brainstem encephalitis is considered." *See* Ex. 6 at 145-154. The January 13, 2016 MRI did not show any significant changes from the initial MRI, but the impression was "Encephalitis or demyelination are suspected." *Id.* at 338. Dr. Curfman, neurologist, explained that while the second MRI did not rule out the glioma, he suspected "an inflammatory process" due to petitioner's rapidly developing symptoms. *Id.* at 133.

The *Gutrecht* article, referenced by Dr. Torntatore, indicates that the initial impression from MRIs in MAID cases is often a brain tumor, but biopsies showed evidence of demyelination. Ex. 30 at 1,5.[19] *Gutrecht* described MAID as "more akin to ADEM," with the exception that lesion is monofocal. *Id.* at 6. The article explained that patients with MAID present with acute onset motor deficits, headaches, dysphagia, some visual field deficits and at times, altered level of consciousnesses. *Id.* at 1. Further, MRIs show a single large, monofocal contrast-enhancing lesions and typical recovery after initiation of treatment (corticosteroid therapy). *Id.* at 5. The course described in *Gutrecht* is similar to petitioner's clinical course in this case. The *Miller et al*[20] article, also submitted by petitioner, describes a 36-year-old woman with a remarkably similar presentation to the hospital as petitioner in this case. Ex. 31. The case report in the *Miller* article

[18] MAID is Monofocal Acute Inflammatory Demyelination

[19] Gutrecht, J et al., *Monofocal Acute Inflammatory Demyelination (MAID): A Unique Disorder Simulating Brain Neoplasm,* 95 Southern Med. J. 1180-1186 (2002). [Ex. 30].

[20] Miller, DH et al., *Acute disseminated encephalomyelitis presenting as a solitary brainstem mass,* 56 J. Neurol. Neurosurg. Psychiatry 920-922 (1993). [Ex. 31],

explains that the patient presented with two-week history of mild headache and nausea accompanied by dysphagia. *Id.* Additionally, the woman described in the *Miller* article had an unsteady gait for five days and examination revealed a left Horner's syndrome, gaze evoked bilateral horizontal nystagmus, reduced right facial sensation, diminished gag reflex and mild ataxia. *Id.* The patient's CSF showed elevated white cells and protein. *Id.* While in the hospital, the patient's condition worsened with increasing gait ataxia, along with ataxia of the left sided limbs and she developed aspiration pneumonia and was intubated and ventilated. *Id.* The MRI revealed a mass lesion in the left side of the medulla and pons situated dorsally and adjacent to the fourth ventricle; it displayed uniform gadolinium enhancement. *Id.* A stereotactic MRI guided biopsy of the brainstem lesion revealed multiple small foci of perivascular inflammation and demyelination. *Id.* at 2. The appearances on her MRIs were compatible with perivenous encephalomyelitis and she was treated with high dose intravenous methylprednisolone, but her condition continued to deteriorate over the following two weeks. *Id.* Initially, the *Miller* patient's lesion increased in size with worsening symptoms, but a repeat MRI three months later showed a marked reduction in size of the original lesion with loss of mass effect. *Id.* The authors also noted that after 18-months the patient continued to have severe disequilibrium and limb ataxia. *Id.* The authors of *Miller* explained that because the MRI revealed a solitary enhancing mass lesion, ADEM was considered "unlikely" because there was only one lesion (not disseminated) and it was a mass lesion. *Id.* However, the biopsy showed perivenous inflammation and demyelination suggestive of ADEM. *Id.* The authors wrote that, "The evolution of [the] MRI lesion in our patient is certainly typical of an inflammatory/demyelinating CNS lesion." *Id.* In this case, no biopsy was done, but the imaging and disease progression were almost identical to the patients in *Miller* and *Gutrecht.*

Dr. Leist opined that petitioner's MRIs did not support demyelination for two reasons. Ex. C at 2. First, he argued that the lesion did not display diffusion changes during "the acute phase of the presentation," specifically on January 10, and January 13, 2016. Ex. C at 2 (citing Ex. 6 at 334-34, 338). Dr. Leist cited to an article by *Mabray et al.*,[21] which evaluated the usefulness of "apparent diffusion coefficient (ADC) values and conventional MRI features to differentiate tumefactive demyelinating lesions and high-grade gliomas. Ex. G at 1. *Mabray* explains that tumefactive demyelinating lesions are generally larger than 2 cm and exhibit varying degrees of mass effect, which can simulate the appearance of an aggressive brain tumor. *Id.* at 1. The authors of *Mabray* hypothesized that ADC values would differ in tumefactive demyelinating lesions and high-grade brain tumors, which could assist in diagnosing tumefactive demyelinating lesions noninvasively. *Id.* at 2. The authors found that ADC values can be used to differentiate TDLs from brain tumors and that ADC values were higher in TDLs compared to other brain tumors (gliomas and lymphomas). *Id.* at 8. Additionally, the authors noted that incomplete rim enhancement on MRIs had "the highest specificity of the tested single variables," to diagnose tumefactive lesions from other types of brain tumors. *Id.* In this case, the ADC was not calculated, but the MRI showed incomplete rim enhancement. *See* Ex. 6 at 78. Further, the *Mabray* article explained that TDLs, high-grade gliomas, and CNS lymphoma "can all have areas of reduced diffusion." *Id.* Thus, areas of reduced diffusion alone on an MRI does not provide any significant insight to the differential diagnosis and petitioner's physicians did not appear to attach particular

[21] Mabray, M. et al., *Performance of apparent diffusion coefficient values and conventional MRI features in differentiating tumefactive demyelinating lesions from primary brain neoplasms,* 205 A. J. Roenterol. 1075 (2015). [Ex. G].

significance to its appearance when considering his underlying condition. Further, the lack of restricted diffusion appeared to be most useful in this case to discount the likelihood of a vascular infarct which was initially being considered. This diagnosis was largely eliminated from petitioner's differential diagnosis by the results of the CT angiogram which found "patent cervical and intracranial vasculature. No evidence of high grade cervical or proximal intracranial arterial stenosis, occlusion, filling defect or aneurysm." *See* Ex. 6 at 84.

Dr. Leist's second critique of the MRIs was the finding of continued peripheral enhancement from January 10 through the March 3, 2016. Ex. C at 2 (citing Ex. 6 at 334-34, 338; Ex. 5 at 23). The March 3, 2016 MRI, the enhancement was described as mild peripheral enhancement on the left lateral margin. Ex. 2 at 28. Dr. Leist opined that in demyelinating lesions, enhancement is "a transient feature" which typically "subsides within a month." Ex. C at 2. In support of this proposition, he cited *Cotton's*[22] study of 26 patients with relapsing-remitting MS, who underwent MRI imaging each week for 8 weeks, then every other week for the next 16 weeks, and monthly thereafter. Ex. E at 1. In the *Cotton* study, enhancement for an individual new lesion lasted on average 3.07 weeks (median, 2 weeks). *Id.* Despite this average, *Cotton* also observed lesion enhancement for up to fifteen (15) weeks. *Id.* at 6. Moreover, Cotton noted that larger lesion size correlated with longer duration of enhancement. Ex. E at 6-7.

Here, Dr. Tornatore correctly observed that petitioner's March 3rd MRI showed only "mild" continued enhancement. Ex. 5 at 23. Petitioner's initial lesion was also relatively large. *See* Ex. 6 at 334 ("involving the inferior aspect of the left pontine tegmentum and extensively involving the amygdala, with involvement of the entire left half of the medulla and the bilateral medullary periods"). Dr. Leist acknowledged that comparison of the two brain MRIs from January 2016, the next MRI on March 3, 2016, showed *improvement* of the signal abnormality. Ex. C at 2 (citing Ex. 5 at 23). Another MRI was not conducted until June 14th, at which point the lesion was "entirely resolved with no enhancement." Ex. 8 at 10-11. Based on the available information, petitioner's lesion enhancement was significantly improved by March 3, and appears to have been within the range of enhancement reported by *Cotton*.

Petitioner's MRIs are more consistent with what was described in the literature for MAID. The lesion was noted to be a longitudinally continuous lesion primarily affecting the left half of the brainstem. Additionally, its progressive disappearance over a period of a few months is also consistent with what is described in the literature for ADEM, and the rarer MAID.

4. CSF Profile

Dr. Tornatore opined that the findings of immunoglobulins and inflammatory cells would be unlikely in a direct infection of the brainstem; those findings were more indicative of autoimmune demyelination. Ex. 27 at 6, 8 (citing Ex. 6 at 304, 329-30). Dr. Leist did not address these specific findings.

[22] Citing Cotton F. et al., *MRI Contrast Uptake in New Lesions in Relapsing-Remitting MS Followed at Weekly Intervals*, 60 Neurol. 640 (2003) [Ex. E].

Dr. Tornatore opined that the absence of red blood cells also supported autoimmune demyelination. Ex. 27 at 8 (lack of citation in the original). In response, Dr. Leist cited *Chaudhuri* and *Kennedy*,[23] who indeed note that only 20% of viral encephalitis cases will have excess red blood cells in CSF. Ex. C at 4, citing Ex. F at 4-5.

The *Chaudhuri* article describes viral encephalitis as a medical emergency with fever, headache, and rapidly advancing symptoms often leading to loss of consciousness. *Id.* *Chaudhuri* states that the diagnosis should be made based on positive evidence and that it is not a diagnosis of exclusion. Ex. F at 2. The article notes that Herpes Simplex Virus (HSV 1 and 2) are the most common causes of viral encephalitis. *Id.* It was Dr. Leist's opinion that petitioner's sinusitis, which was caused by a bacterial infection, was the most likely cause of petitioner's encephalitis. Ex. A at 7. He stated that, "During [petitioner's] sick visit on January 9, 2016, he was diagnosed with sinusitis and started on antibiotics." *Id.* Dr. Leist also observed that a "large retention cyst in the left maxillary sinus were visualized on the CT performed January 10, 2016." *Id.* However, petitioner explained that he had a two-year history of congestion and just blew his nose several times a day. *See* Ex. 6 at 202. As petitioner described these symptoms, they appear to have been mild and stable, and had not changed in or around the time of the onset of his encephalopathy. The Urgent Care physician described the sinusitis as "subacute' and found no congestion, sore throat, cough or, shortness of breath Further, the maxillary sinus cyst appeared identical to what was seen on the CT scan six years before. *Id.* at 206. Significantly, Dr. Douglas Nucklos, the ENT who treated petitioner, noted that petitioner's neurological symptoms were unrelated to the chronic sinusitis. *Id.* Additionally, petitioner was extensively tested for multiple pathogens at both Parkview and the Cleveland Clinic, all of which were negative.

Finally, Dr. Leist noted that early ADEM (which as noted above, he disputed as a specific diagnosis in this case) "may" feature polymorphonuclear leucocytes – but those were not found in Mr. Hofer's CSF sample obtained two days after onset of overt clinical symptoms. Ex. C at 2 (citing Ex. F at 4). A review of *Tenembaum* and *Noorbakhsh* do not mention polymorphonuclear leucocytes in their extensive descriptions of ADEM. *See* Ex. 23 [24]; Ex. 24.[25] It appears that such a finding would be an occasional one rather than a necessary one to diagnose ADEM.

Based on my review of the experts' opinions and the relevant literature submitted, the petitioner's CSF findings are non-specific and by themselves do not show support for a demyelinating diagnosis, nor do they identify a viral or bacterial pathogen. To completely rule out an alternative cause other than demyelination, a brain biopsy would have been required, which did not occur in this case.

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[23] Chaudhuri A. & Kennedy P.G.E., *Diagnosis and Treatment of Viral Encephalitis*, 78 Postgrad Med. J. 575 (2002) [Ex. F].

[24] Noorbakhsh F., Johnson F., et al., *Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features*, 26 Neurol. Clin. 759, 759 (2008) [Ex. 23].

[25] Tenembaum S. et al., *Acute Disseminated Encephalomyelitis: A Long-Term Follow-Up Study of 84 Pediatric Patients*, 59 Neurology 1224, 1224 (2002) [Ex. 24].

5. IVIg Treatment

Petitioner also argued that an autoimmune etiology was likely because the five-day IVIg course "showed improvement." Motion at 31. Respondent argued that IVIg delivered only "slight improvement," e.g., a "minimal" response. Response at 4-5, 8-9. The parties first cited a January 20, 2016, record, which provides that petitioner "feels like he has *not* improved" – but that was only the second day of IVIg. Ex. 6 at 231 (emphasis added). More relevant are records from *after* completion of IVIg – which reflect subjectively improved vision, facial symmetry, and vocal strength. Ex. 6 at 983 (contemporaneous record). At the Cleveland Clinic, petitioner also reported that after completion of IVig that he had some improvement in facial weakness, complete improvement of diplopia, and some improvement in gait and swallowing. Ex 5 at 10. The treating providers recognized that IVIg may have been somewhat beneficial. The most direct reference is by the Cleveland Clinic infectious disease specialist Dr. Bhimraj, who opined that petitioner's radiological and clinical improvement "could be from the treatments he received (steroids, IVIg, or the antimicrobials) or he is improving by himself." Ex. 6 at 36.

6. Explanation of CNS Autoimmune Demyelinating Injuries

Dr. Tornatore recognized from the start of the case that the "inflammation was monofocal (i.e., restricted to one area, in this case the brainstem)." Ex. 20 at 18. Dr. Tornatore opined that this restriction to one extensive location in the brainstem was "the only difference" distinguishing this injury from ADEM which usually presents with similar but disseminated lesions. *Id.* The clinical presentation was "remarkably similar" to ADEM with features including: "MRI findings which are initially profound but resolve over time; cerebrospinal fluid results consistent with an inflammatory response originating outside of the nervous system; and subsequent residual deficits." *Id.* at 17-18. Dr. Tornatore reasoned that the similar clinical presentation pointed to a similar *nature* of injury and therefore, a similar *theory* of vaccine causation. *Id.* at 18-19. Therefore, he opined that "a discussion of ADEM helps to inform this case." *Id.* at 18.

ADEM is defined as an inflammatory demyelinating disease of the central nervous system ("CNS") characterized by an acute onset and a monophasic course. Ex. 24; *see also Dorland's* at 1224.[26] "[ADEM] features an autoimmune attack on the myelin sheath of the [CNS], resulting in inflammation and swelling in the brain and spinal cord. When the myelin is damaged, nerve impulses can slow or stop, causing a range of neurological problems. Symptoms can include fever, headache, vomiting, tremors, seizures, and paralysis."[27] Depending on the location of the lesion or lesions, ADEM may present with headaches, vomiting, ataxia, cranial nerve palsy, acute hemiparesis and other symptoms. Ex. 24 at 4.

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[26] *Dorland's* (defining ADEM as "an acute or subacute encephalomyelitis *characterized by perivascular lymphocyte and mononuclear cell infiltration* and *demyelination*… It is believed to be a manifestation of *an autoimmune attack on the myelin of the central nervous system…* Called also acute perivascular myelinoclasis, postinfectious e., post-vaccinal e., and acute disseminated, post-infectious, or post-vaccinal *encephalitis*") (emphasis added).

[27] As concisely summarized by now-Chief Special Master Corcoran in a previous entitlement opinion in which the petitioner retained Dr. Tornatore and the respondent retained Dr. Leist to opine on ADEM. *Caruso v. Sec'y of Hum. Servs.*, No. 15-0200V, 2017 WL 5381154, *12 (Fed. Cl. Spec. Mstr. Oct. 18, 2017). From my review of the medical literature submitted in the present case, *Hofer*, this basic understanding of ADEM has not changed.

In ADEM, the selective involvement of the CNS cannot be explained. Ex. 22 at 5.[28] However, within the CNS, "any portion" can be affected. Ex. 20 at 18.[29] White matter is more common, but lesions in cortical gray matter and basal ganglia have also been reported. Ex. 23 at 4.

Dr. Leist, citing to *Tenembaum* article, objected to any discussion of ADEM, reasoning that ADEM is defined as an injury to *disseminated* areas of the CNS. Ex. A at 7 (citing Ex. 24 at 1). That classic definition of ADEM is not in dispute. The relevant question is whether the injury must be spatially disseminated throughout the CNS to be demyelinating in nature.

The *Tenembaum* article does not address whether a large monofocal, demyelinating lesion can cause a condition similar or identical to ADEM, but for the lack of dissemination. *Tenembaum* was a "long-term follow-up study of 84 pediatric patients" diagnosed with ADEM – designed to identify subgroups, evaluate outcomes, and distinguish certain cases where the course involved a relapse (biphasic, therefore termed BDEM) from multiple sclerosis ("MS"). Ex. 24 at 1, 9. The authors concluded that even BDEM "may be distinguished from childhood MS on the basis of clinical, biochemical, and neuroimaging follow-up." *Id.* at 1231. Similarly, the *Noorbakhsh* article submitted by Dr. Tornatore, includes a table of the "differential clinical and diagnostic features" of ADEM versus MS. Ex. 23 at 14.

Dr. Leist's literature has a similar focus. For example, he submitted a 2003 review of ADEM, which states: "*The most important issue* associated with the diagnosis of ADEM is – can this disorder be diagnosed with certainty and differentiated from the initial manifestation of multiple sclerosis [MS]?" Ex. A, Tab 4.[30] ADEM and MS are both demyelinating in nature. However, ADEM is a monophasic illness with favorable long-term prognosis while MS is relapsing and remitting, with new lesions developing over time. *Id.* at 1, 14. Therefore, "the differentiation of ADEM from a first attack of [MS] has prognostic and therapeutic implications." *Id.* Petitioner's condition was monophasic, and no further lesions appeared, MS was ruled out. The question becomes whether the literature has identified monophasic cases of demyelination that present similarly to ADEM but for the single location of the lesion.

The literature supports that spatial dissemination is not necessary to prove that a CNS injury is demyelinating. In *Tenembaum*'s study of pediatric ADEM, dissemination was required for inclusion and specifically excluded patients with acute monosymptomatic syndromes such as transverse myelitis or optic neuritis and thus does not address the central question in this case. Ex. 24 at 3. In contrast, *Noorbakhsh* states that transverse myelitis is a "common clinical presentation of post-infectious or post-vaccinal ADEM that is characterized by focal inflammation of the spinal cord." Ex. 23 at 5. *Garg* states that ADEM is "related" to more "restricted form[s] of acute, inflammatory, demyelinating disorders" including transverse myelitis [TM], optic neuritis [ON],

[28] Johnson R., *The Pathogenesis of Acute Viral Encephalitis and Post-Infectious Encephalomyelitis*, 155 J. Infect. Dis. 359 (1987) [Ex. 22].

[29] Dr. Tornatore used the synonym "neuraxis" for "the central nervous system." *Compare* Ex. 20 at 18 and *Dorland's*.

[30] Garg R.K., *Review: Acute Disseminated Encephalomyelitis*, 79 Postgrad J. Med. 11 (2003) [Ex. A-4].

and cerebellitis." Ex. A, Tab 4 at 2. Thus, while the classic presentation of ADEM is disseminated, the literature demonstrates that monofocal presentations do occur and cause a symptom complex and disease course similar to ADEM.

In his second report, Dr. Tornatore maintained that an acute monofocal inflammatory event in the CNS can be demyelinating, thus representing a *forme frustre* of ADEM. Ex. 27 at 3. The *Gutrecht, Miller and Kepes* articles also support the diagnosis of a monofocal ADEM-like condition referred to as MAID.

As detailed above, *Mille*r reported on an adult patient admitted for a clinical course including a two-week history of mild headache and nausea, as well as dysphagia, nasal regurgitation, and worsening gait ataxia (unsteadiness). Ex. 31 at 1. MRI revealed that the brainstem featured an enhancing solitary mass lesion – which was "unusual," but "occasionally occur[red]" in ADEM. *Id.* Subsequent stereotactic MRI-guided biopsy of the brainstem lesion "revealed multiple small foci of perivascular inflammation of demyelination… suggestive of ADEM." *Id*. A repeat MRI three months later found that the lesion was non-enhancing and markedly reduced in size, which *Miller* felt was "certainly typical of an inflammatory/demyelinating CNS lesion." *Id.* While his patient was given acyclovir, Miller felt that the pathological features and negative viral serology made it unlikely that the injury was caused by herpes simplex. *Id.* More likely was "a localized form of ADEM, akin to well-recognized syndrome of post-infectious transverse myelitis [TM] and optic neuritis [ON], in which immunopathogenic mechanisms are probably important." *Id. Miller* concluded that "ADEM should be considered in the differential diagnosis of sub-acute MRI enhancing brainstem masses." *Id.* at 3. Dr. Tornatore opined that patient described in *Miller* bore "remarkable similarities to petitioner's case from a clinical standpoint." Ex. 27 at 3.

The *Kepe*s article described 31 patients with the acute onset of neurological symptoms; a large focal brain lesion resembling a tumor; biopsy and histological confirmation that the lesion was demyelinating in nature; significant improvement with corticosteroids; and no evidence of new lesions. Ex. 29 at 4, 5.[31] *Kepes* highlighted, under a subheading concerning "history of stimulation of the immune system," that one patient "received a flu vaccine 10 days before the onset of her clinical symptoms," which was like two other patients previously reported in other literature. *Id.* at 6. These three patients suggested "an allergic phenomenon." *Id.* at 8. *Kepes* also wrote that such cases resembled ADEM and/or post-infectious or post-vaccination encephalomyelitis ("PPE"). *Id.* at 18.

Gutrecht similarly described the phenomenon of "a single, large, monofocal, contrast-enhancing brain lesion with associated edema and mass effect" which when biopsied, revealed acute demyelination. Ex. 30. *Gutrecht* wrote some patients eventually develop additional lesions and are diagnosed with MS. Patients without such progression are diagnosed with monophasic acute inflammatory demyelination ("MAID"). Corticosteroid therapy can be clinically beneficial. *Id.* at 1, 5. MAID's "precise nosological classification… in the spectrum of acute demyelinating diseases remains uncertain," but it may represent "a singular, less aggressive *forme frustre* of

[31] Kepes J.J.. *Large Focal Tumor-Like Demyelinating Lesions of the Brain: Intermediate Entity Between Multiple Sclerosis and Acute Disseminated Encephalomyelitis?: A Study of 31 Patients*, 33 Ann. Neurol. 18 (1993) [Ex. 29].

ADEM." *Id.* at 1185-86. Dr. Tornatore summarized that this clinical entity is recognized in the medical literature and that it fit the available evidence about petitioner. Ex. 27 at 4.

In response, Dr. Leist opined that inflammatory brain lesions can occur without an identifiable cause; it is very unusual for a demyelinating injury such as ADEM to present as a single brain lesion and with mass effect; and that biopsy is required to confirm the nature of injury. Ex. C at 3 (citing *Miller et al.); see also* Response at 8. However, Dr. Leist did not rebut Dr. Tornatore's opinion, which is well-supported by the aforementioned literature, that a CNS monofocal acute inflammatory injury can be autoimmune and demyelinating in nature.

Ideally, the diagnosis of demyelination would have been confirmed by a brain biopsy, however, the physicians at the Cleveland Clinic determined that the risks of a brain biopsy was unnecessary, given petitioner's symptoms were improving, there is preponderant evidence that petitioner suffered a demyelinating condition. Both the opinion of Dr. Tornatore and the medical literature, as summarized above, support a finding that petitioner suffered a demyelinating injury to his brainstem similar to ADEM, which was described as MAID-a monofocal acute inflammatory demyelination. A viral encephalitis, as proposed by Dr. Leist, is considerably less likely given the course of petitioner's symptoms, the negative pathogen tests, and the opinions of petitioner's treating physicians. As such, I find that petitioner's condition was consistent with MAID, or a monofocal, demyelinating condition.

B. *Althen* Prong One

1. Introduction and 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 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. In *Althen*, the Federal Circuit recognized that even though the petitioner's claim involved 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. Petitioner's Expert Dr. Tornatore

Dr. Tornatore opined that the subject flu vaccine can cause CNS autoimmune demyelination. He primarily cited literature addressing ADEM. I have accepted his explanation that ADEM is the more commonly recognized diagnostic entity – and that it is likely to inform the understanding of rarer and/or more recently identified *monofocal* autoimmune demyelination in the CNS. I find that similarly, literature pertaining to ADEM and its potential causation, including by flu vaccine, is relevant to understanding related injuries.

Dr. Tornatore opined that ADEM can be triggered by a variety of antigens including vaccinations. Ex. 20 at 18. He submitted literature which supports this proposition: "ADEM is more commonly preceded by a viral infection, with measles, varicella, rubella, mumps, and influenza being the more frequently reported infections." Ex. 23 at 6. "Vaccination against viral etiologies has significantly decreased the incidence of viral cases of ADEM, and the risk imposed by vaccines themselves is significantly less than natural infections." *Id.* at 16. Nonetheless, *Noorbakhsh* observes that ADEM can be "post-vaccinal," including after flu vaccines. *Id.* at 7, 9. Dr. Leist's submitted literature also recognizes potential association between ADEM and flu vaccines. Ex. A, Tab 4 2. *Garg* provides, "Another common variant of ADEM is that which follows vaccination (postimmunization encephalomyelitis)." *Id.* at 1. Moreover, *monofocal* CNS autoimmune demyelination was reported to be preceded by the administration of swine flu vaccine in two cases, and after flu vaccine in another case. Ex. 29 at 4, 10.

Dr. Tornatore opined: "Vaccinations, including against influenza, are nothing more than a collection of antigens intended to trigger a protective immune response in the host. In rare events however, the immune response to the vaccination results in humoral and cellular responses that target not only the vaccine antigens, but self-antigens which bear a resemblance to the vaccine antigens. When these self-antigens are targeted by this aberrant autoimmune response, the result is an inflammatory cascade which results in organ damage." Ex. 20 at 18. This "primary immune-mediated inflammatory reaction" can lead to activation of self-reactive lymphocytes, with subsequent infiltration of the target organ. This mechanism is termed molecular mimicry. Ex. 20 at 18, citing Ex. 23 at 9, 11-12. (expressly applying this mechanism to post-vaccinal ADEM); *see also* Resp. Ex. A, Tab 4 at 2 (stating "existing evidence suggest that ADEM results from a transient autoimmune response against myelin or other autoantigens, possibly, via molecular mimicry or by non-specific activation of an autoreactive T cell clone.").

Dr. Tornatore stated that the *Noorbakhsh* article provided an explanation of how the flu vaccine, through molecular mimicry could induce ADEM. Ex. 20 at 18. The *Noorbakhsh* article provides:

> Molecular mimicry is one of the proposed mechanisms by which pathogens might lead to autoimmune responses. If self-and non-self-pathogen derived antigens share the same epitopes, presentation of the epitope to the immune system with concomitant activation of a primary innate immune-mediated inflammatory reaction might lead to activation of self-reactive lymphocytes, with subsequent infiltration of the target organ.

Ex. 23 at 22-23. Dr. Tornatore acknowledged that no target antigens in the nervous system have been specifically identified for ADEM, consistent with the medical literature. But stated, "Given that there are thousands of potential antigens expressed in the nervous system, it is highly probable that sequence homology can be found between any vaccine antigen and brain antigens." Ex. 20 at 18. Dr. Tornatore also stated that "Receptors on B and T cells that were once thought to have a high level of specificity for individual foreign antigens are now known to recognize peptide sequences that share no homology," where a single T cell receptor may recognize thousands of different peptide sequences. *Id.* at 21.[32] Either mechanism can lead to a primary immune mediated

[32] Mason D., *A Very High Level of Cross-Reactivity is an Essential Feature of the T-Cell Receptor*, 19 Immunol. Today. 395 (1998) [Ex. 26].

inflammatory reaction with infiltration of the target organ. In this case, Dr. Tornatore's theory was primarily focused on myelin basic protein, which has been identified as a likely target for molecular mimicry resulting in ADEM.

In his second report, Dr. Tornatore reiterated his opinion that the influenza vaccine, through molecular mimicry, can result in an immune response where specific antigens are targeted. Ex. 27 at 8. He stated that research at Harvard "demonstrated that influenza peptides could induce the activity of myelin basic-protein-specific T cell clones," which represents a "biologically accepted mechanism of influenza vaccine-induced demyelination." *Id.*

3. Respondent's Expert Dr. Leist

Dr. Leist did not respond to much of the discussion introduced above – such as a vaccine's intended effect in the immune system; the potential for aberrant autoimmune response following receipt of a vaccine; the explanation of molecular mimicry as involving sequence and/or structural homology; the degree of homology required or how it would be identified; the likelihood of molecular mimicry between the flu vaccine and myelin basic protein or other self-antigens; or other potential mechanisms. *See generally* Exs. A, C.

Dr. Leist opined that "based on reputable information, it is not known that influenza vaccine can cause ADEM." Ex. C at 3. He provided only two literature citations. First, in 2012, the Institute of Medicine ("IOM") concluded that the available evidence was "inadequate to accept or reject a causal relationship" between flu vaccine and either encephalitis or encephalopathy. Ex. A at 7.[33] The excerpted pages do not address ADEM, which is the focus of the theory being evaluated. Regardless, the referenced IOM report often reaches this conclusion, which is appropriate for purposes of public health policy and the general safety of vaccines. The cases presented in this program involve rare adverse events that are not readily identified by epidemiology. The causation of these rare events following vaccination are supported by immunological theories, most prominently including molecular mimicry and T cell degeneracy.

Second, Dr. Leist introduced a 2016 study by *Baxter*[34] which utilized Vaccine Safety Datalink ("VSD") data from 2007 – 2012, capturing nearly 19 million doses of trivalent and quadrivalent inactivated flu vaccine ("IIV"). Ex. D at 1-2. The study only recognized ADEM if 1) that diagnosis was entered into the medical records by a treating neurologist; *and* 2) a reviewing neurologist concurred that medical record evidence satisfied the Brighton group's diagnostic criteria for ADEM. *Id.* at 1457. 56 cases of ADEM were identified. *Id.* at 1460. In four (4) of those cases, inactivated flu vaccine was administered 5 – 28 days prior to onset (defined as "the most likely interval… to result in a demyelinating illness"). *Id.* at 5. Baxter calculated a 0.137 excess risk of ADEM within 5 – 28 days after inactivated flu vaccine was administered, with a confidence level of 95% (-.26 to .63). *Id.* Baxter concluded that this risk was not statistically significant.

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[33] Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* (Stratton et al., eds., 2012), 299-301 [Ex. A-6].

[34] Citing Baxter R. et al., *Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis*, 63 Clin. Infect. Dis. 1456 (2016) [Ex. D].

Compare id. (finding that in contrast, an excess risk of 0.385 for ADEM after Tdap vaccine *was* statistically significant). Nevertheless, the study did identify a small increase in risk for ADEM following the influenza vaccination while finding no excess relative risk between multiple other vaccines.

While Dr. Leist did not discuss the Brighton Criteria, which are a research criterion designed to assure only the inclusion of clear cases for research studies such as the *Baxter* study, variant presentations such as that of petitioner are excluded. Given the small number of rare events under consideration the exclusion of some variant presentations could likely affect the statistical significance of the findings.

Ultimately, Dr. Leist concluded that petitioner's neurological condition was "brought on by the pathogens associated with sinusitis," without articulating how exactly the pathogens from a viral infection could cause ADEM. Ex. C at 3.

4. Analysis and Conclusion Regarding *Althen* Prong One

Petitioner has provided preponderant evidence of a sound and reliable medical theory explaining how the influenza vaccine can cause ADEM. This finding is supported by Dr. Torntore's opinion and the medical literature. Respondent argued that "Dr. Leist is better qualified to opine… on the body's immunological reaction to a flu vaccination" and on the potential for vaccine causation of the subject injuries. Response at 9; *but see* Reply at 5 (arguing that Dr. Tornatore is also well-qualified to opine regarding immunology). Respondent's argument about Dr. Tornatore's qualifications to opine on vaccine causation is accorded no weight as both doctors are well qualified by education and experience to opine on the subject matter of this case.

MAID, a monofocal version of ADEM, is considered an autoimmune condition. (INSERTCITATION). Dr. Tornatore's theory of molecular mimicry to induce autoimmune diseases is one that has been found to be sound and reliable by myself and other special masters. *See Introini v. Sec'y of Health & Human Servs.,* No. 20-176V, 2022 WL 16915818 (Fed. Cl. Spec. Mstr. Oct. 19, 2022) (finding that molecular mimicry is a sound and reliable theory for inducing autoimmune diseases); *Gross v. Sec'y of Health & Human Servs.,* 2022 WL 9669651 (Fed. Cl. Spec. Mstr. Sept. 22, 2022) (accepting molecular mimicry as a theory for inducing demyelinating conditions); *Koller v. Sec'y of Health & Human Servs.,* No 16-439V, 2021 WL 5027947 (Fed. Cl. Spec. Mstr. Oct. 8, 2021). The theory of molecular mimicry he articulated is also one that was endorsed in both the *Noorbakhsh* and *Garg* articles. *See* Ex. 23 at 12; Ex. A, Tab 4 at 2. As articulated in the *Noorbakhsh* article:

> Molecular mimicry is one of the proposed mechanisms by which pathogens might lead to autoimmune responses. If self-and non-self-pathogen derived antigens share the same epitopes, presentation of the epitope to the immune system with concomitant activation of a primary innate immune-mediated inflammatory reaction might lead to activation of self-reactive lymphocytes, with subsequent infiltration of the target organ. Although subject to thymic negative selection, some self-reactive lymphocytes including lymphocytes reactive to different components of myelin still persist in adult immune system. Sequence similarity

searches to find common linear epitopes between different ADEM-inducing pathogens and myelin basic protein have yielded some results.''

Ex. 23 at 11-12.

While Dr. Tornatore did not identify specific sequence homology between the influenza vaccine and myelin basic protein, he also credibly explained that T cells can recognize thousands of different peptide sequences, which would generate an autoimmune response in the nervous system. As explained in the *Mason* article, "While it is evident that there is a degree of specificity among T cells for the peptide-MHC complexes that they recognize, recent observations reveal that there is considerable cross reactivity such that one TCR can recognize a number of different peptides that do not necessarily show strong sequence homology." Ex. 26 at 1. Additionally, the *Garg* article supports the proposition that ADEM can be triggered by a "nonspecific activation of an autoreactive T cell." Ex. A, Tab 4 at 2. Specific mimicries have been shown only in a limited number of autoimmune diseases, however, molecular mimicry is still a primary theory of vaccine or infection-based causation of autoimmune disease.

Dr. Leist did not explicitly disagree with Dr. Tornatore theory of molecular mimicry as a mechanism for inducing autoimmune diseases of the central nervous system. Rather, Dr. Leist argued that the *Baxter* study, an epidemiological study, found "no risk of a demyelinating injury associated with the flu vaccine," and that the IOM found "evidence was inadequate to accept or reject a causal conclusion" between an inactivated influenza vaccine and encephalitis. Response at 9; Ex. A at 7. For the reasons discussed above, the reliance on the *Baxter* study is unpersuasive in this case. I find that the literature discussing molecular mimicry as a recognized theory of autoimmune causation is sufficient to explain how the immune reaction to a vaccine can cause an autoimmune disease such as ADEM or MAID.

Additionally, and importantly, requiring epidemiologic studies to prove causation "impermissibly raises a claimant's burden under the Vaccine Act." *Capizzano*, 440 F.3d 1317, 1326. As the Federal Circuit observed, "As a general matter, epidemiological studies are designed to reveal statistical trends only for a carefully constructed test group. Such studies provide no evidence pertinent to persons not within the parameters of the test group." *Moberly*, 592 F.3d 1315, 1324. Petitioner's need to provide a medical theory of causation that needs to be corroborated by medical literature *or* epidemiological evidence. *Knudsen*, 35 F3d. at 548 (emphasis added). As petitioner's variant presentation of ADEM would not have been included within the test group in the *Baxter* study but did appear in other medical literature presented by Dr. Tornatore, the *Baxter* study does not preclude a conclusion of causation in this case.

The literature in this case, filed by both parties, recognizes the acceptance of molecular mimicry as a recognized theory of autoimmune causation sufficient to explain how the immune reaction to the influenza vaccine can result in ADEM or MAID. The additional explanation of T-cell degeneracy is also a recognized theory of autoimmune causation. As such, petitioner, through Dr. Tornatore, has presented a sound and reliable theory, supported by the medical literature. Accordingly, petitioner has established *Althen* prong one.

C. *Althen* Prong Two/ Factor Unrelated

1. Introduction and Legal Standard

To fulfill *Althen* prong two, petitioner must present "a logical sequence of cause and effect showing that the vaccination was the reason for his 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 ("a petitioner must provide a reputable medical or scientific explanation that pertains specifically to [his or her] case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Hum. Servs.,* 9556 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; *Grant*, 956 F.2d at 1148.

If petitioner makes out a *prima facie* case, the burden shifts to respondent to establish that the injury was due to "factors unrelated to the administration of the vaccine." Section 13(a)(1)(B). However, a "factor unrelated" cannot be an "idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition." Section 13(a)(2)(A). A factor unrelated may be "as documented by the petitioner's evidence or other material in the record, include infection… which have no known relation to the vaccine involved, but which in the particular case are shown to have been the agent or agents principally responsible for causing the petitioner's… injury." Section 13(a)(2)(B).

Whether the burden has shifted necessarily depends on a weighing of the particular case record. In either scenario, the burdened party's showing must be by a preponderance of the evidence. *Knudsen*, 35 F.3d at 549 (stating that "the standards that apply to a petitioner's proof of actual causation in fact in off-table cases should be the same as those that apply to the government's proof of alternative actual causation in fact"). In *Knudsen*, the petitioner made a *prima facie* showing of a Table injury, so the burden undoubtedly shifted to respondent. However, the case stands for some relevant principles applicable either to *Althen* prong two (petitioner's burden) or alternative cause (respondent's burden). Namely in *Knudsen*, the Federal Circuit held that an established "viral infection" can serve as a more likely alternative cause of the petitioner's injury, even if the viral infection "is not in the particular case specifically identified by type or name," so long as that viral infection is proved to be "principally responsible" for causing the injury at issue. *Id.* at 549-50. The Federal Circuit also recognized the potential of concurrent non-causal infection, and rejected a "unity" theory – e.g., that *all* symptoms and injuries suffered around the time of the subject vaccination must be explained by the vaccination. *Id.* Finally, the Federal Circuit reasoned that the "bare statistical fact" that the subject injury reportedly occurred more often after viral infection than after the subject vaccine was "not evidence in a particular case." *Id.* at 550. The Federal Circuit therefore remanded *Knudsen* for the special master to further consider all of the evidence presented in that particular case, regarding causation by the subject vaccine versus a documented but unspecified viral infection. *Id.* at 550-51.

Thus, other potential causes of injury "can be relevant not only to the factors unrelated" defense, but to whether a *prima facie* showing has been made that the vaccine caused the injury in question. *De Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1353 (Fed. Cir. 2008); *see*

also Walther, 485 F.3d 1146; *Pafford*, 451 F.3d 1352. It is particularly appropriate to consider any "elephant in the room – the presence of *compelling evidence of a different cause* for the injury in question." *Stone*, 676 F.3d at 1380 (affirming that respondent had established that a documented SCN1A gene mutation represented a more likely alternative cause). However: "[T]he focus should be on the contemporaneous circumstances of the injury that are unrelated to the vaccination… petitioners need only address those alternative causes that can be identified in the evidentiary record." *Contreras*, 107 Fed. Cl. 280, 298. It is unfair to require a petitioner to identify and then eliminate all known causes, and the fact that the injury is idiopathic in some or many cases does not frustrate a petitioner's ability to prevail. *Id.* (citing *Pafford*, 64 Fed. Cl. 19, 36, *aff'd*, 451 F.3d 1352).

2. Analysis and conclusion of *Althen* prong two/alternative causation

Dr. Tornatore opined that petitioner's clinical course was consistent with post-vaccinal acute disseminated encephalomyelitis, except that it was monophasic and involved a single large lesion. Ex. 20 at 17. He explained that initially petitioner developed profound neurologic symptoms that were also reflected in the MRI of his brainstem which showed inflammation; there was resolution of the inflammation in subsequent MRIs; and petitioner suffered from residual neurological deficits. *Id.* at 18. He also stated that petitioner's neurological symptoms began within a month of receiving the vaccination, which is consistent with "an autoimmune event triggered by a vaccine." *Id.* at 20.

Respondent is correct to observe that the petitioner's treating physicians at Parkview did not explicitly connect the flu vaccine to his neurological condition, they also did not rule it out. Importantly, the hospital records also include a notation that petitioner had not had a flu vaccine which was carried through in multiple parts of the record. *See* Ex. 6 at 60, 100, 224. It is unclear whether the treating physicians had any knowledge that petitioner had received the flu vaccine approximately one month prior the onset of the neurological symptoms and it would be pure speculation as to whether they would have considered it as a causative factor. But what is clear from the records, is that the incorrect notation that petitioner had not had an influenza vaccine recently was carried forward throughout the course of his hospital stay.

Additionally, when petitioner's acute phase of his condition had been resolved, neurologist Dr. Gupta considered the flu vaccine as the possible cause of petitioner's condition in the differential diagnosis. Dr. Gupta wrote, "It is unknown if patient had brainstem encephalitis or a nonspecific episode of brainstem demyelination which may have been…mediated following influenza vaccination." Ex. 8 at 4. Dr. Tornatore interpreted this notation from Dr. Gupta as clear evidence that a "post-vaccinal demyelination" was considered "given that no other etiology could be identified." Ex. 27 at 2. Respondent asserted that Dr. Gupta was simply "casting a wide net of potential causes," when no other etiologic causes were identified, and that is not the same as concretely opining that the vaccine was the causative agent. However, the lack of a concrete opinion from a treating provider connecting the vaccine and the injury is not required under *Althen* two. Instead, petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. *Capizzzano*, 440 F.3d at 1325. The medical opinion provided by Dr. Tornatore credibly explains that petitioner's condition was consistent with a post-vaccinal autoimmune

neurological condition of MAID and his opinion was supported by the medical literature filed in this case.

Respondent also argued that the record includes evidence of a "concomitant infection" and that petitioner's expert did not appropriately rule-out that cause, and that petitioner did not rule out "unknown causes," of ADEM-MAID. Response at 14-15. To put it another way, respondent is arguing that petitioner needs to rule out both a possible concomitant infection and then also *all* other unknown causes of the injury to demonstrate a logical sequence of cause and effect. Neither of these arguments are persuasive.

If petitioner makes out a *prima facie* case, the burden shifts to respondent to establish that the injury was due to "factors unrelated to the administration of the vaccine." Section 13(a)(1)(B). However, a "factor unrelated" cannot be an "idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition." Section 13(a)(2)(A). A factor unrelated may be "as documented by the petitioner's evidence or other material in the record, include infection… which have no known relation to the vaccine involved, but which in the particular case are shown to have been the agent or agents principally responsible for causing the petitioner's… injury." Section 13(a)(2)(B).

Dr. Leist suggested that a "sinus infection" was likely the causative agent of petitioner's neurological condition, rather than the flu vaccine. Ex. C at 4. Dr. Leist opined that certain pathogens that cause sinusitis in chronic smokers, such as petitioner, are "known causes of encephalitis and are known to be associated with ADEM." *Id.* He referenced multiple articles to support his position.

First, *Brook* and *Hausfled,* examined the microbiology of sinuses in smokers and non-smokers with acute and chronic maxillary sinusitis. Ex. A-2 at 2.[35] The authors stated that patients complained of "facial pain, frontal headache, purulent nasal discharge, fever, and malaise." *Id.* None of these symptoms were present in the petitioner. The patients described with "acute infection" had symptoms that lasted between 10 to 30 days and those with chronic infection had symptoms for more than 90 days. *Id.* There were 84 patients with chronic sinusitis that were smokers. *Id.* at 3. The authors found "the predominance of *s. pneumoniae, H influenzae, M catarrhails, group A beta-hemolytic streptococci,* and *s aureus"* in patients with acute sinusitis. *Id.* at 4. Another article by Brook explains that most sinus infections are caused by viruses (most frequently rhinovirus, influenza, and parainfluenza). Ex. A-1 at1. The viral phase usually lasts up to 10 days and ends with complete recovery in most individuals. *Id.* "However, some individuals (estimated at 0.5%) develop an acute bacterial infection generally caused by facultative aerobic bacteria (e.g., *streptococcus pneumoniae, haemophilus influenzae, moraxella catarrhalis*). If the acute infection does not resolve, anerobic bacteria that originate from the oral flora can become the predominant pathogens." *Id.* The chronic form ("CRS") has "significant[ly] differen[t]" microbiology and is predominated by *staphylococcus aureus, staphylococcus epidermis,* and anaerobic Gram-negative bacteria. *Id.* at2. In a separate article, *Brook* conducted endoscopic cultures of various patients with sinusitis. Smokers had higher isolation rates of *staphylococcus*

[35] Brook, I, and Hausfeld, J, *Microbiology of Acute and Chronic Maxillary Sinusitis in Smokers and Nonsmokers,* 120 Annals of Otology, Rhinology & Laryngology, 707-712 (2011). [Ex. A-2].

aureus, its methicillin-resistant form ("MRSA"), and beta-lactamase-producing bacteria ("BLPB"). *Id.*

Separately, *Granerod* writes that encephalitis has been associated with viral infections including cytomegalovirus, Epstein-Barr, enterovirus, herpes, and varicella. Ex. A-5 at 2. Potential bacterial culprits include bacillus anthracis; bartonella hensalae; borrelia; chlamydia; legionella; leptosporosis; listeria; mycoplasma pneumonia; mycobacterium tuberculosis; salmonella; streptococcus pneumoniae; and streptococcus pyogenes. *Id. Garg* provides a similar list of identified viruses preceding ADEM. Ex. A-4 at 2. ADEM has been associated with viral infections including measles, mumps, influenza A or B, hepatitis A or B, herpes simplex, human herpes virus E, varicella, rubella, Epstein-Barr virus, cytomegalovirus, and HIV. *Id.* "Other" infections include mycoplasma pneumoniae ("the main bacterial infection… implicated" in ADEM), chlamydia, legionella, campylobacter, and streptococcus. *Id.* at1-2. Petitioner's cultures for all the pathogens listed above were negative. *See* Ex. 5 at 43-45. Petitioner's treating physicians also tested petitioner for other pathogens, including borrelia burgdorferi (Lyme), West Nile Virus, and syphilis, which were also negative. Ex. 5 at 43-47. The extensive pathogen work-up by petitioner's treating physicians ruled out many possible viral or bacterial causes of an autoimmune neurological condition such as ADEM. In short, the record does not include any evidence of identified pathogens from the articles referenced by Dr. Leist that have been known to cause ADEM or encephalitis. Nor did petitioner experience any of the symptoms of chronic or acute sinusitis that were described in the articles. Petitioner told ENT, Dr. Douglas Nuckols that he had some sinus drainage in the mornings, but that his symptoms had largely remained unchanged for a long period of time. *See* Ex. 6 at 202. When petitioner presented to Dr. Shawn Kidder on January 9, 2016, petitioner complained of a headache in the back and top of head. Ex. 4 at 2. The location of this headache is different from the location of headaches associated with sinusitis, as described in the *Brook* article. *See* Ex. A-2 at 2. At that same appointment, petitioner was negative for "sinus pain," and the physical exam noted that his nose was "normal." *Id.* at 4.

Thus, Dr. Leist's alternative cause of a sinus infection rests solely on the CT scan of petitioner's sinuses which found a cyst on the maxillary sinus. The CT scan did reveal a cyst in the left maxillary sinus and he was diagnosed with mild bilateral sinusitis. Ex. 6 at 333; Ex. 7 at 4. He was evaluated by ENT, Dr. Douglas Nuckols, who compared petitioner's most recent CT to one from 2010 and stated, "Chronic sinusitis/left maxillary mucus retention cyst…Findings chronic and present at similar degree from CT in 2010." *Id.* at 206. Petitioner reported to Dr. Nuckols that he would blow his nose several times a day, but his symptoms were year-round. *Id.* at 202. After reviewing the CT scan, listening to petitioner's history and doing a physical exam, Dr. Nuckols diagnosed petitioner with chronic sinusitis and wrote, "Unrelated to current symptoms, but should be addressed." *Id.* at 206. He prescribed a course of antibiotics for petitioner and recommended that petitioner begin Flonase, for allergy relief. *Id.*

Dr. Tornatore argued that the influenza vaccine was the only differing input to petitioner's immune system in the weeks prior to the onset of his neurological symptoms and that petitioner did not have any "symptoms referable to the upper respiratory tract." Ex. 27 at 4. The medical records support Dr. Tornatore's opinion. Contrary to respondent's argument, Dr. Tornatore *did* consider whether another immune stimuli, such as a sinus infection could further stimulate an already activated immune system in the development of the brainstem inflammatory

demyelination. *See* Ex. 27 at 4. However, Dr. Tornatore correctly observed that ENT, Dr. Nuckols did not attribute petitioner's neurological condition to the finding of sinusitis. *Id.* Importantly, nothing in the medical records suggests that petitioner was suffering from any symptoms of sinusitis or an acute sinus infection. Petitioner did not endorse a sinus headache, or significant nasal congestion and his physical examination of the upper respiratory passages was negative. Thus, it does not appear that there is "significant" evidence of a concomitant infection, given that petitioner was negative for pathogens associated with the onset of ADEM, he had no symptoms of an active sinus infection, and the treating ENT did not associate the finding of the sinusitis with petitioner's neurological injury. I find that Dr. Leist's opinion that the alternative cause for petitioner's neurological injury does not meet the standard of more likely than not.

Instead, petitioner's clinical course and presentation was consistent with Dr. Tornatore's opinion of how the influenza vaccine, through molecular mimicry, can result in an autoimmune demyelinating event in the central nervous system presenting as MAID. The medical literature referenced by Dr. Tornatore describes a rapid onset of symptoms, including headache, nausea and unsteadiness in walking in ADEM. *See* Ex. 23 at 4; Ex. 31 at 1. Petitioner's presenting symptoms included a headache emanating from the area of the lesion, vomiting, dizziness and difficulty with walking. Ex. 4 at 2; Ex. 7 at 1. Further, the large T2 hyperintensity that extended over the left side of petitioner's brainstem and beyond with disabling symptoms consistent with injury to that area of the brain were like those seen in the literature describing MAID. *See* Ex. 31 at 1-2 (MRI revealed a mass lesion in the left side of the medulla that displayed uniform gadolinium enhancement). Additionally, the resolution of petitioner's T2 hyperintensities over the course of six months, is also consistent with ADEM or MAID described in the medical literature. *See* Ex. 31 at 3 (repeat MRI of patient with monofocal lesion showed a marked reduction in size). No alternative causes for the injury were identified by his treaters or were otherwise evident from the record. Tests for infectious agents were entirely negative. For these reasons, petitioner has established preponderant evidence to establish *Althen* prong two.

D. *Althen* Prong Three

To fulfill *Althen* prong three, a petitioner must establish that the subject vaccine and the injury's temporal relationship is "proximate," meaning "medically-acceptable." *Althen* at 1281. This showing requires "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*, 539 F.3d 1347, 1352. 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.*

In this case, petitioner received the subject flu vaccine on December 15, 2016. He developed a headache on or around Christmas – December 25, 2016 in the top and back of his head-not in his frontal sinuses. He developed rapid worsening attributable to his acute neurological injury (including nausea, dizziness impaired balance, vomiting, and primarily occipital headache) on or around January 9, 2016.

Petitioner's expert, Dr. Tornatore, opined that this temporal association "would certainly be consistent with an autoimmune event triggered by a vaccine." Ex. 20 at 19. In evaluating the

timing, Dr. Tornatore again analogized petitioner's injury to ADEM (which apart from being disseminated, is accepted to be sufficiently similar in nature as addressed above). *Id.* He opined that "ADEM typically appears with the onset of neurologic symptoms 2 to 30 days after the occurrence of a preceding infection or vaccination." *Id.*, citing Tenembaum (full citation *supra* at n. 24) at 1225. In his supplemental report, Dr. Tornatore reiterated: "[G]iven that MAID and ADEM are near identical entities, I would anticipate that the immunopathogenesis and clinical manifestations post-vaccination would follow similar time courses." Ex. 27 at 8-9.

Dr. Leist did not dispute this onset for petitioner's injury or the temporal association with the flu vaccination. *See generally* Exs. A, C. He did not dispute that the timing would be medically acceptable – and indeed, seemed to embrace it – agreeing that "post-infectious neurologic symptoms typically appear 2 – 30 days after a preceding infection." Ex. C at 3. He also cited *Baxter* for the proposition that ADEM has a "primary exposure window of 5-28 days following vaccination." *Id.*, citing *Baxter* (full citation *supra* at n. 34) at 1456. Dr. Leist's only relevant objection was that allegedly causal, unrelated and unidentified pathogens were introduced during this same time period[36] – thereby impliedly endorsing that the timing of onset would be medically acceptable, and not arguing that the timeframe for a vaccine-induced immune response would be any different.

Both experts agreed that the onset of ADEM or MAID for a vaccine induced immune response of 2-30 days is appropriate. As the onset of petitioner's condition occurred approximately 10 days post-vaccination, within the timeframe described in the literature, petitioner has established *Althen* prong three.

V. Conclusion

Based on a review of the entire record and consistent with the above opinion, petitioner has established entitlement to compensation. Further deadlines and guidance pertaining to the damages phase will follow separately.

IT IS SO ORDERED.

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

[36] I have not accepted this factual assertion, in the above analysis of *Althen* prong two.