In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: May 15, 2023

GERTRUDE SMILO, Administratix of the estate of JOSEPH G. SMILO, deceased,	*	PUBLISHED
Petitioner,	*	No. 18-1585V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Influenza ("Flu") Vaccine; Myasthenia Gravis; Causation-in-Fact; Significant Aggravation.
Respondent.	*	

Jeffrey A. Golvash, Golvash & Epstein, LLC, Pittsburgh, PA, for Petitioner.
Naseem Kourosh, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On October 12, 2018, Gertrude Smilo ("Petitioner"), Administratix of the Estate of Joseph G. Smilo ("Mr. Smilo"), deceased, filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

et seq. (2018)[2] alleging that Mr. Smilo developed myasthenia gravis which was caused-in-fact, or in the alternative, significantly aggravated by an influenza ("flu") vaccination administered on October 17, 2016. Petition at Preamble (ECF No. 1). Respondent filed his Rule 4(c) Report on October 30, 2019, arguing against compensation, stating "this case is not appropriate for compensation under the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 25).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has failed to provide preponderant evidence that Mr. Smilo's myasthenia gravis was caused by or significantly aggravated by his flu vaccination. Thus, Petitioner has failed to satisfy her burden of proof under Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274,at 1278 (Fed. Cir. 2005) and Loving v. Secretary of Health & Human Services, 86 Fed. Cl. 135, 142-44 (2009). Accordingly, the petition shall be dismissed.

II. ISSUES TO BE DECIDED

The parties stipulate that Mr. Smilo received a flu vaccination on October 17, 2016, at the age of 63, and that he died on April 6, 2017. Joint Submission, filed Aug. 4, 2022, at 1 (ECF No. 59). His death certificate identified "his 'immediate cause' of death as liver failure and hepatocellular carcinoma [("HCC")]." Id. Other significant conditions that contributed to his death but did not result "'in the underlying cause' of death [were] myasthenia gravis, septic shock, and multiple organ failure." Id. They further agree that Mr. Smilo "suffered from myasthenia gravis." Id.

As a threshold matter, the parties dispute whether Petitioner meets the severity requirement under Vaccine Act § 11(c)(1)(D).[3] Petitioner's Motion for Ruling on the Record ("Pet. Mot."), filed Aug. 5, 2022, at 23 (ECF No. 60); Resp. Response to Pet. Mot. ("Resp. Response"), filed Sept. 21, 2022, at 13-21 (ECF No. 62); Pet. Reply to Resp. Response ("Pet. Reply"), filed Oct. 5, 2022 (ECF No. 63). Specifically, the parties dispute whether Petitioner has shown Mr. Smilo "(ii) died from the administration of the vaccine, or (iii) suffered such illness, disability, injury, or condition from the vaccine which resulted in inpatient hospitalization and surgical intervention." § 11(c)(1)(D)(ii)-(iii); see Joint Submission at 2; Pet. Mot. at 23; Resp. Response at 13-21; Pet. Reply at 1-4.

There is also a factual dispute. The parties disagree as to the onset of Mr. Smilo's myasthenia gravis, specifically whether onset was before or after the flu vaccination

[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 (2018). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

[3] Although this issue was not mentioned in the parties' joint submission, the parties addressed it in their respective briefs, and thus, the undersigned finds it is appropriate to resolve the issue.

administered on October 17, 2016. Joint Submission at 1; Pet. Mot. at 9, 17; Resp. Response at 21.

Regarding causation, the parties dispute whether Petitioner has proven by preponderant evidence that the flu vaccination can cause or significantly aggravate myasthenia gravis, and that it did so here.[4] Joint Submission at 1. Further, they dispute whether Petitioner has proven by preponderant evidence the standards articulated in Althen/Loving. Pet. Mot. at 23; Resp. Response at 13. Lastly, the parties dispute whether Petitioner has proven by preponderant evidence that Mr. Smilo's death was the result of his flu vaccination. Joint Submission at 2.

III. PROCEDURAL HISTORY

Petitioner filed a petition on October 12, 2018, followed by medical records on November 30, 2018 and an expert report from Dr. George Alan Small on December, 3, 2018. Petition; Pet. Exhibits ("Exs.") 1-15. On September 27, 2019, Petitioner filed additional medical records. Pet. Exs. 16-17. Respondent filed his Rule 4(c) Report, arguing against compensation on October 30, 2019. Resp. Rept. at 2.

From April 2020 to August 2021, Petitioner filed expert reports from Dr. James N. DeAngelo and Dr. Small, medical records, and affidavits, and Respondent filed expert reports from Dr. Eric Lancaster. Pet. Exs. 18, 45-47, 55, 61-62; Resp. Exs. A, C-D. Thereafter, this case was referred to alternative dispute resolution ("ADR") in September 2021, but by November, this case was removed from ADR proceedings. Order Referring Case to ADR dated Sept. 23, 2021 (ECF No. 43); Order Concluding ADR Proceedings dated Nov. 2, 2021 (ECF No. 44).

This case was reassigned to the undersigned on February 7, 2022. Notice of Reassignment dated Feb. 7, 2022 (ECF No. 47). The undersigned held a status conference on February 17, 2022 to discuss next steps. Order dated Feb. 17, 2022 (ECF No. 48). On March 21, 2022, Respondent indicated he was not amenable to settlement discussions. Resp. Joint Status Rept., filed Mar. 21, 2022, at 1 (ECF No. 49). The parties indicated that they wished to file supplemental expert reports before resolving entitlement through a ruling on the record. Id.

Petitioner filed a supplemental expert report from Dr. Small on March 13, 2022, and Respondent filed a supplemental expert report from Dr. Lancaster on June 17, 2022. Pet. Ex. 63; Resp. Ex. E. In August 2022, Petitioner filed her motion for a ruling on the record. Pet. Mot. Respondent filed his response on September 21, 2022, and Petitioner filed a reply on October 5, 2022. Resp. Response; Pet. Reply.

This matter is now ripe for adjudication.

[4] If Mr. Smilo's symptoms of myasthenia gravis preceded vaccination, then Petitioner agrees that the case involves a significant aggravation claim. Pet. Mot. at 8. If, however, onset occurred after vaccination, Petitioner confirms that she is pursuing a "new injury claim," or causation-in-fact. Id.

IV. MEDICAL TERMINOLOGY

Myasthenia gravis is a rare disease, but "the most common disorder of the neuromuscular junction." Resp. Ex. E, Tab 1 at 1.[5] It is "a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs." Pet. Ex. 12 at 1.[6] The "hallmark" of the illness is "muscle weakness that worsens after periods of activity and improves after periods of rest." Id. "Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often . . . involved in the disorder." Id. Generally, the initial symptom is "weakness of the eye muscles," which manifests as "drooping of one or both eyelids (ptosis)." Id. at 2. Others may have difficulty swallowing. Id. The extent of muscular weakness ranges from a localized type of weakness involving the eye muscles to a severe form that affects the muscles responsible for breathing. Id. Since weakness is a vague and common symptom of many illnesses, the diagnosis may be delayed in those who have a mild presentation or when weakness is limited to "a few muscles." Id. at 4.

"Most patients—roughly two-thirds—initially present with ocular symptoms: ptosis and/or diplopia without pupillary abnormalities. Weakness of the eye muscles is often asymmetrical and variable." Resp. Ex. E, Tab 1 at 2. Of the patients who present with ocular symptoms, many will develop more generalized disease. Id. at 5. Myasthenia gravis crisis is likely to occur early in the disease process, and "usually within the first [three] years following diagnosis." Id. "Myasthenic crisis is a complication of myasthenia gravis characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation." Resp. Ex. E, Tab 2 at 1.[7] Approximately 15-20% of patients who have myasthenia gravis will experience a crisis at least once. Id. "The median time to first myasthenic crisis from onset of [myasthenia gravis] ranges from 8-12 months. However, myasthenic crisis may be the initial presentation [] in one-fifth of patients." Id.

"Myasthenia gravis is caused by an error in the transmission of nerve impulses to muscles. It occurs when normal communication between the nerve and muscle is interrupted at the neuromuscular junction—the place where nerve cells connect with the muscles they control." Pet. Ex. 12 at 1. "[A]ntibodies (immune proteins) block, alter, or destroy the receptors for acetylcholine at the neuromuscular junction, which prevents the muscle from contracting." Id. In most patients with the illness, this error in transmission "is caused by antibodies to the acetylcholine receptor [("AChR" or "AchR")] itself." Id.

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[5] Michael K. Hehir & Nicholas J. Silvestri, Generalized Myasthenia Gravis: Classification, Clinical Presentation, Natural History, and Epidemiology, 36 Neurology Clinics 253 (2018).

[6] Myasthenia Gravis Fact Sheet, Nat'l Inst. of Neurological Disorders & Stroke, https://www.ninds.nih.gov/health-information/disorders/myasthenia-gravis (last modified July 6, 2018).

[7] Linda C. Wendell & Joshua M. Levine, Myasthenic Crisis, 1 Neurohospitalist 16 (2011).

Treatment is aimed at improving muscle weakness. Pet. Ex. 12 at 4. Medications that decrease the "breakdown of acetylcholine at the neuromuscular junction" are used to increase muscle function. Id. at 4-5. Immunosuppressive drugs are given to "suppress[] the production of abnormal antibodies." Id. at 5. For severe symptoms, plasmapheresis and intravenous immunoglobulin ("IVIG")[8] can be given, but their effectiveness is limited in duration. Id.

V. FACTUAL SUMMARY

A. Summary of Relevant Facts[9]

1. Pre-Vaccination Records

Mr. Smilo was born on May 31, 1953. Pet. Ex. 1 at 1. Prior to vaccination, he had a history of hypertension, low back pain, and esophageal reflux. Pet. Ex. 3 at 1, 7; Pet. Ex. 6 at 12, 18.

In May 2016, Mr. Smilo was seen by his primary care physician, Dr. George Gavin, for treatment of malaise, cough, nasal congestion, and fever. Pet. Ex. 3 at 23, 26. Dr. Gavin diagnosed an upper respiratory infection. Id. at 26. Mr. Smilo saw Dr. Gavin again on August 22, 2016, complaining of dysphagia,[10] hoarseness, and cough. Id. at 18. Dr. Gavin ordered an esophagogastroduodenoscopy ("EGD").[11] Id. at 20.

Approximately one week later, on September 1, 2016, Mr. Smilo was seen by Dr. Jose Mejia at Excela Health Medical Group for lower back pain. Pet. Ex. 3 at 14, 16. Mr. Smilo reported "trouble with swallowing." Id. at 14. Mr. Smilo returned to see Dr. Mejia on September 26, 2016 for his lower back pain and reported "hoarseness and pain on swallowing." Id. at 10.

Mr. Smilo also saw his optometrist, Paul F. Ives, O.D., beginning in 2013 for eye examinations and to monitor his ocular hypertension, pre-glaucoma condition. Pet. Ex. 45 at 16. In 2015, Mr. Smilo was diagnosed with mild primary open angle glaucoma. Id. at 12.

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[8] IVIG is immune globulin used to treat various immunodeficiency disorders. Immune Globulin Intravenous (Human), Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=78975 (last visited Apr. 24, 2023).

[9] This summary contains only facts related to Mr. Smilo's symptoms, onset, and diagnosis of myasthenia gravis, as those are most pertinent. Additional factual summaries are set forth in the parties' expert reports and briefs. See, e.g., Pet. Mot. at 1-7; Resp. Response at 2-10.

[10] Dysphagia means "difficulty in swallowing." Dysphagia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=15265 (last visited Apr. 24, 2023).

[11] EGD is the "endoscopic examination of the esophagus, stomach, and duodenum." Esophagogastroduodenoscopy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=17345 (last visited Apr. 24, 2023).

Thereafter, he saw Dr. Ives on a regular basis for glaucoma, through February 2017. See id. at 2-12. His records do not contain any references either before or after vaccination to drooping eyelids or ptosis.

2. Vaccination and Post-Vaccination Records

Mr. Smilo saw Dr. Gavin on October 17, 2016 for follow-up visit and reported that he continued to have intermittent lower back pain. Pet. Ex. 3 at 1-8. Magnetic resonance imaging ("MRI") of the lumbar spine performed on October 11, 2016 showed degenerative and postoperative changes of the lower back, with some impingement on the S1 nerve root. Id. at 4-5. An EGD performed on September 28, 2016 showed chronic gastritis and esophagitis. Id. at 5-7. Physical examination revealed weakness of the right lower extremity and abnormal deep tendon reflexes of the left lower extremity. Id. at 3. The flu vaccination at issue was administered to Mr. Smilo at this visit. Id. at 7.

Approximately one month later, on November 17, 2016, Mr. Smilo returned to Dr. Gavin's office and was seen by Dr. Courtney Floyd. Pet. Ex. 4 at 27-29. Chief complaint was "throat sore, eye drooping [one] week, slurred speech [one] week. Onset of symptoms was [one] week[] ago. Patient report[ed] . . . tightness in throat." Id. at 27 (emphasis omitted). Dr. Floyd's records also documented that Mr. Smilo had "right eye droop [three] months." Id. (emphasis omitted). Dr. Floyd documented that Mr. Smilo reported that at the "[e]nd [of] September after endoscopy noticed he felt like he had something in this throat he couldn't swallow[,] slurred speech just started last night[,] eyelid drooping has been more chronic." Id. Physical examination revealed "right eyelid drooping." Id. at 28. Dr. Floyd assessed Mr. Smilo with "stroke-like symptoms," and referred him to Dr. Roger Goebel at the emergency department ("ED") at Latrobe Hospital for further diagnosis and treatment. Id. In addition to a possible stroke, Dr. Floyd also questioned whether Mr. Smilo had "myasthenia or [B]ell's palsy." Id. As part of her plan, she wrote that if Mr. Smilo was "cleared from stroke [symptoms], can return for workup of the eyelid." Id.

Mr. Smilo presented to the ED that day, on November 17, 2016, and was initially seen by the triage nurse, James Jellison, Registered Nurse ("RN"). Pet. Ex. 5a at 40. Nurse Jellison wrote that Mr. Smilo complained of

> slurre[d] speech and right sided eye droop. [Patient] state[d] he has been having problems with his right eye for months, but had some difficulty with speech for the last week . . . . [Patient] state[d] has had problems feeling like he had a phlegm ball in the back of his throat[,] so he had an EGD at the end of September, state[d] that he has been having worsening problems just this week however.

Id. Mr. Smilo reported that the "onset time was [three] months ago. The symptoms came on gradually. The symptoms [had] worsened since onset." Id. at 43. Diagnostic studies were ordered and initiated. Id. at 45-47.

Subsequently, Mr. Smilo was seen by Dr. Goebel. Pet. Ex. 5a at 54. Dr. Goebel took a history of present illness, stating that "onset time was [three] week(s) prior to arrival. . . . The

symptoms came on gradually. The symptoms [had] worsened since onset." Id. at 55. The history also stated that "[three] months ago noticed [right] drooping eyelid, slurred speech last week, and last night at dinner wife noted mouth drooping. He has also had trouble swallowing since his endoscopy in September." Id. (emphasis omitted).

Diagnostic computerized tomography ("CT") scan relative to the liver showed "[q]uestionable areas of more focal decreased density . . . in the hepatic dome near the caudate and right hepatic lobe . . . . The caudate lesion may exhibit mild mass effect and measures up to 5.5 cm." Pet. Ex. 5a at 60. Radiologist Dr. Neal Klitsch's impression was that the liver findings could represent fatty infiltration, "but focal hepatic lesions [were] not excluded particularly in the caudate. Follow-up contrast MRI of the liver [was] recommended." Id. It does not appear that follow-up MRI was done.

After diagnostic testing, Mr. Smilo was discharged home with instructions to follow up with Dr. Gavin. Pet. Ex. 5a at 53. Discharged diagnosis was right mild ptosis, hoarse voice, and dysphagia. Id. at 63. Mr. Smilo saw Dr. Gavin on December 7, 2016 and reported that "[h]is dysphagia and voice disturbance ha[d] worsened," but that "[h]is ptosis [was] not as bad as he [was] no longer taping up his right upper lid." Pet. Ex. 4 at 22. Mr. Smilo also reported a weight loss of 30 pounds over the past three months. Id. "He ha[d] developed dysphagia for solids and liquids." Id. Physical examination revealed that Mr. Smilo had "a bulbar voice." Id. at 24. "[M]ild right upper lid ptosis" was also noted. Id. Dr. Gavin ordered additional diagnostic testing and a referral to neurology. Id.

Mr. Smilo saw neurologist Dr. Louis W. Catalano on December 12, 2016. Pet. Ex. 6 at 12. Dr. Catalano documented that Mr. Smilo "report[ed] onset of trouble swallowing in August 2016. . . . In November 2016[,] he had onset of difficulty with speech and increased difficulty with swallowing. . . . His wife noted right eyelid drooping in the spring of 2016; worse [November 2016] and he complained of his eyelid blocking vision." Id. Neurological examination revealed "[n]asal speech[,] [s]evere dysarthria/severe dysphagia[,] [m]yopathic facies," and "[b]ilateral ptosis, R[ight]>L[eft] with fatigue." Id. at 13. Dr. Catalano's impression was "[m]yasthenia [g]ravis, ocular-bulbar, acute." Id. at 14. Diagnostic bloodwork was ordered and treatment with IVIG and Mestinon[12] was initiated. Id. The bloodwork showed elevated levels of AChR antibodies. Id. at 15, 18.

On December 22, 2016, Mr. Smilo presented to the ED complaining of weakness to the point that he was having "increased difficulty holding up his head and swallowing." Pet. Ex. 5a at 127. Petitioner also completed of "an increased cough the past day." Id. He was seen by Dr. Michael Zorch, whose history noted that Mr. Smilo complained of "generalized weakness that began some time ago." Id. at 137 (emphasis omitted). Recently, he had experienced "increasing

[12] Mestinon, a trademark for pyridostigmine bromide, "acts by inhibiting destruction of acetylcholine and so facilitating transmission of impulses across the neuromuscular junction; used as a cholinergic in the symptomatic treatment of myasthenia gravis." Mestinon, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=30704 (last visited Apr. 24, 2023); Pyridostigmine Bromide, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=42398 (last visited Apr. 24, 2023).

generalized weakness," "difficulty swallowing food," "difficulty breathing[,] which is exacerbated with exertion," and "deteriorating speech." Id. After bloodwork revealed low potassium, Dr. Zorch admitted Mr. Smilo for treatment of his hypokalemia and myasthenia gravis with acute exacerbation. Id. at 139, 142.

Admitting history and physical examination by Dr. Melissa Stewart noted that Mr. Smilo had issues swallowing, and that he had experienced a "choking episode." Pet. Ex. 5a at 109. Since his condition had worsened, Mr. Smilo had not been able to tolerate solids and had a choking episode when trying to swallow on the day of admission. Id. Therefore, he was to be kept NPO, or nothing by mouth. Id. at 111, 123. Gastroenterology was consulted for a percutaneous endoscopic gastrostomy[13] ("PEG") tube placement "for nutritional support." Id. at 112.

During hospitalization Mr. Smilo was initially monitored in the intensive care unit ("ICU") due to his risk of respiratory decompensation and need for intubation. Pet. Ex. 5a at 113, 118. Intubation was not required, but he did require bilevel positive airway pressure ("BiPaP") due to his low oxygen saturation levels. Id. He was treated with IVIG and steroids, and ultimately improved so that he could be transferred out of ICU to a medical floor bed. Id. at 125. His dysphagia, however, did not improve, and he had a PEG tube inserted on January 3, 2017, for treatment of his "progressive dysphagia. He failed swallow evaluation and modified barium swallow and had aspiration and penetration."[14] Id. at 113, 125. Mr. Smilo's discharge note dated January 11, 2017 stated, "Dysphagia. The patient had a PEG tube placed. This is all secondary to his myasthenia gravis." Id. at 125; see also id. at 112, 165, 172, 174, 224 (explaining how Petitioner's myasthenia gravis led to his dysphagia, which required placement of a PEG tube since Petitioner was not improving with only a feeding tube).

Consents for anesthesia and the EGD and PEG tube were signed by Mr. Smilo on January 3, 2017. Pet. Ex. 5a at 301-03. In the consents, the PEG tube procedure was described as "[p]lacement of a feeding tube through the abdominal wall into the stomach . . . with endoscopic guidance." Id. at 302.

The operative report for his PEG tube insertion was dated January 3, 2017 and identified Dr. Ted A. Matthews as the surgeon and Dr. Douglas Klions as the gastroenterologist for the procedure. Pet. Ex. 5a at 271-74. The procedure performed was "[EGD] with placement of a gastrostomy tube." Id. at 273. Dr. James I. Sadler was the anesthesiologist, and the anesthesia

[13] Gastrostomy is a "surgical creation of an artificial opening into the stomach." Gastrostomy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=19901 (last visited Apr. 24, 2023).

[14] Modified Barium Swallow Study performed December 29, 2016 was abnormal. Pet. Ex. 5a at 103-04. "Throughout the examination there was penetration of barium with undercoating of the epiglottis. There was occasional aspiration . . . ." Id. at 103.

type was monitored anesthesia care ("MAC"), and midazolam,[15] lidocaine,[16] and propofol[17] were administered. Id. at 281. The operative note stated that "[a]fter adequate sedation," an endoscope was placed by Dr. Klions (gastroenterologist) and "positioned in the midportion" of the stomach, "directed towards the anterior abdominal wall." Id. at 274. "A polypectomy snare was passed into the stomach by [Dr. Klions], [and] opened fully . . . ." Id. On the outside of the abdominal wall, "[t]he overlying skin was anesthetized with lidocaine and 0.5 cm incision was made at the [] site. The introducer needle with overlying catheter was passed through this incision and into the stomach under visualization with the endoscope. The needle and catheter were [] captured by the endoscopy snare." Id. "The gastrostomy tube . . . was pulled [] into the stomach until the 3 cm mark of the gastrostomy tube was noted at skin level and adequate placement of the [] tube [was achieved]. The patient tolerated the procedure well and was taken to post anesthesia care unit in good condition." Id. "There were no intraoperative complications. Dr. Matthews and Dr. Klions were present . . . for the entirety of the procedure." Id. Anesthesia postoperative note from Dr. Sadler documented that the patient had "[n]o [a]pparent [c]omplications" of anesthesia. Id. at 284.

During his hospitalization, Mr. Smilo had a syncopal episode due to autonomic dysreflexia, and collapsed after voiding. Pet. Ex. 5a at 125, 160. He was treated with intravenous fluids. Id. at 125. On January 11, 2017, Mr. Smilo was discharged, and on January 13, he was admitted to Westmoreland Inpatient Rehabilitation. Id.; Pet. Ex. 7a at 7. From January 13 to January 21, 2017, Mr. Smilo received "aggressive" physical therapy, occupational therapy, and speech therapy. Pet. Ex. 7a at 7, 9. He began taking Imuran (azathioprine), an immunosuppressant medication for treatment of his myasthenia gravis, daily during this time. Id. at 308-09, 342. During rehabilitation, he "progressively improved," and was stable on discharge. Id. at 9.

Mr. Smilo saw Dr. Gavin and Dr. Catalano in January 2017. Pet. Ex. 4 at 10-12; Pet. Ex. 6 at 6-10. At these visits, Mr. Smilo's condition was stable; however, he continued to have difficulty swallowing. Pet. Ex. 4 at 10, 12; Pet. Ex. 6 at 6, 9. His PEG tube remained in place. Pet. Ex. 4 at 10; Pet. Ex. 6 at 6, 9. Medical records from these visits listed PEG tube placement under Mr. Smilo's surgical history. Pet. Ex. 4 at 11; Pet. Ex. 6 at 7. He was still taking Imuran (azathioprine). Pet. Ex. 4 at 11; Pet. Ex. 6 at 8.

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[15] Midazolam is "used as an antianxiety agent and muscle relaxant." Midazolam, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=31529 (last visited Apr. 24, 2023).

[16] Lidocaine is "a drug having anesthetic, sedative, analgesic, anticonvulsant, and cardiac depressant activities, used as a local anesthetic." Lidocaine, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=28237 (last visited Apr. 24, 2023).

[17] Propofol is "a short-acting anesthetic and sedative used in induction and maintenance of general anesthesia and also for sedation, as during diagnostic procedures or in patients in intensive care units." Propofol, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=41263 (last visited Apr. 24, 2023).

On March 20, 2017, laboratory testing revealed abnormal liver enzyme levels (elevated alkaline phosphatase, aspartate aminotransferase ("AST"), alanine transaminase ("ALT")) and elevated bilirubin levels. Pet. Ex. 3 at 87. Mr. Smilo was diagnosed with "[a]cute cholestatic jaundice" by Dr. Gavin, who suspected the cause was Mr. Smilo's medication azathioprine. Pet. Ex. 4 at 1, 3. Dr. Gavin discontinued the medication and ordered additional lab work and diagnostic testing. Id. at 3. Abdominal CT performed on March 28, 2017 showed a "large 8 cm central hepatic mass with marked intrahepatic and extrahepatic biliary ductal dilation [("IHBDD")]" and "minimal ascites." Pet. Ex. 3 at 113-14 (emphasis omitted). The CT also showed that Mr. Smilo's PEG tube had dislodged, specifically the "balloon of the percutaneous gastrostomy tube appear[ed] extraluminal to the stomach." Id. at 114.

Mr. Smilo saw hepatobiliary surgical oncologist Dr. David Geller on April 3, 2017. Pet. Ex. 8 at 1. Dr. Geller reviewed the CT scan and wrote that the PEG tube balloon "[was] outside the stomach" and would "need to be replaced." Id. Dr. Geller noted a 70 pound weight loss, "scleral icterus[,][18] and deep jaundice."[19] Id. The CT showed a "giant 8 cm central liver mass" and "massive IHBDD." Id. Dr. Geller's diagnosis was "large central liver HCC with obstructive jaundice." Id. He opined that Mr. Smilo was "not [an] operative candidate," and that "[p]rognosis [was] guarded." Id.

That day, Mr. Smilo was admitted to the University of Pittsburgh Medical Center for "obstructive jaundice and PEG tube malfunction." Pet. Ex. 16a at 6. An endoscopic retrograde cholangiopancreatography ("ERCP")[20] with stent placement and PEG tube replacement procedures were anticipated. Id. On April 3, Mr. Smilo also saw oncologist Dr. Padma Rajagopal, whose impression indicated, "[p]atient report[ed] developing [myasthenia gravis] in the setting of a flu shot in October; however, we do not have full information about diagnosis. Myasthenia gravis has also been reported in [one] case report in the literature as being associated with HCC."[21] Id. at 36, 38.

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[18] Scleral icterus is "a yellow discoloration of the sclerae from hyperbilirubinemia." Scleral Icterus, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=81855 (last visited Apr. 24, 2023).

[19] Jaundice, or icterus, is "a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, mucous membranes, and sclera, with resulting yellow appearance of the patient." Jaundice, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition? id=26548 (last visited Apr. 24, 2023).

[20] An ERCP is "a combination of retrograde and transhepatic cholangiography, done to demonstrate all portions of the biliary tree; it is performed by cannulation of the bile duct and pancreatic duct through the papilla of Vater using a flexible fiberoptic endoscope with retrograde injection of a radiopaque medium." Endoscopic Retrograde Cholangiopancreatography, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=65009 (last visited Apr. 24, 2023).

[21] It is not clear what case report Dr. Rajagopal was referencing, nor does it appear the case report was filed.

Mr. Smilo underwent an ERCP with stent placement and PEG tube replacement on April 4, 2017 by Dr. Mordechai Rabinovitz (surgeon) and Dr. Rohit Das (gastroenterologist). Pet. Ex. 16a at 87; Pet. Ex. 16c at 523. The procedures were done under MAC and Dr. Tomas Drabek was the primary anesthesiologist. Pet. Ex. 16a at 87; Pet. Ex. 16c at 524. Consent forms for the procedures were signed by Mr. Smilo. Pet. Ex. 16a at 26-29.

The ERCP was performed and revealed "markedly dilated right and left intrahepatics." Pet. Ex. 16a at 88. Two stents were placed, in the right and left intrahepatics. Id. The operative note for the PEG tube replacement stated that "[t]here was evidence of a gastrostomy with no G-tube present in the gastric body." Id. at 91. The surgeon "creat[ed] a new tract for G-tube placement" at a different site in the stomach. Id. A "trocar needle was introduced through the abdominal wall and into the stomach under direct endoscopic view," and a G-tube was placed. Id. "The old G-tube was removed[,] and a dressing placed at the site." Id. at 92.

Overnight, after surgery, Mr. Smilo developed hypotension and was transferred to ICU. Pet. Ex. 16a at 40. He had "hemoperitoneum and septic shock." Id. at 41. CT of the abdomen on April 5, 2017 showed a "[l]arge irregular hematoma in the epigastrium near new PEG tube," large liver mass, and hepatic lymphadenopathy, suggesting metastatic spread of the cancer. Id. at 119-20. On April 6, 2017, Mr. Smilo's respiratory status deteriorated, and he was intubated. Id. at 41, 44. He passed away that night at 10:18 pm. Id. at 46-47. The death certificate listed cause of death as liver failure due to HCC. Id. at 46; Pet. Ex. 17 at 1. Other significant conditions contributing to death included myasthenia gravis, septic shock, and multiple organ failure. Pet. Ex. 16a at 46; Pet. Ex. 17 at 1.

3. Vaccine Adverse Event Reporting System ("VAERS") Report

A VAERS report was completed by Dr. Gavin. Pet. Ex. 9 at 1. The report is not dated. See id. The report included the date of vaccination as October 17, 2016; Mr. Smilo's name, address, and telephone; the name of Dr. Gavin's medical practice and contact information; and the vaccination type (flu), manufacturer, lot number, and route and site of administration. Id. The form stated that Mr. Smilo had received six prior doses of the flu vaccination (based on Dr. Gavin's medical records). Id. Dr. Gavin included a description of the adverse event: "[Mr. Smilo] had drooping eyelids, occasional blurred vision, trouble swallowing, slurred speech, all over body was tired, [and] trouble breathing." Id. The adverse event onset date was indicated as October 23, 2016. Id. The form also noted that the adverse event was "[l]ife threatening," and "[r]equired emergency room[] visit" and "[r]esulted in prolong[ed] [] hospitalization." Id.

In addition to the report completed by Dr. Gavin, Petitioner also filed a copy of the report obtained from the National Vaccine Information Center. Pet. Ex. 33. The report stated onset was October 23, 2016, six days after vaccination. Id. at 1. The date of submission was not noted; however, the data was entered on January 27, 2017. Id. The symptoms described were identical to those in the above report, including "drooping eyelids, occasional blurred vision, trouble swallowing, slurred speech, all over body was tired[,] [and] [t]rouble breathing." Id. at 2.

B. Affidavits

1. Affidavit of Petitioner

Mrs. Smilo is the widow of Mr. Smilo and the Petitioner. Pet. Ex. 61 at 1. She executed her affidavit on August 9, 2021. Id. at 2. Petitioner averred that prior to Mr. Smilo's vaccination on October 17, 2016, Mr. Smilo was in good health. Id. at 1. Approximately three weeks after he received the flu vaccination, Mr. Smilo had "tightness in his throat, slurred speech, right eyelid droop, and right sided mouth droop." Id. Petitioner stated that Mr. Smilo did not have these problems prior to vaccination. Id. She explained that Mr. Smilo was diagnosed with myasthenia gravis, his symptoms progressed rapidly, and he passed away on April 6, 2017. Id.

Regarding the records of Dr. Catalano, which stated that Petitioner reported that Mr. Smilo's "right eyelid droop began and/or otherwise was present as early as the spring of 2016, or approximately six [] months prior to his [flu] vaccination," Petitioner explained "[she] do[es] not recall making any such representation to Dr. Catalano or any other medical provider." Pet. Ex. 61 at 2. She further averred that any reference in the medical record stating that the onset of Mr. Smilo's right eye ptosis occurred before vaccination is an "error and/or product of miscommunication." Id.

2. Affidavit of Dr. Gavin

Dr. Gavin executed his affidavit on August 13, 2021. Pet. Ex. 62 at 3. He stated that he was Mr. Smilo's primary care physician for five years before his death. Id. at 1. Prior to his flu vaccination on October 17, 2016, Dr. Gavin averred that Mr. Smilo did not "complain of fatigue/muscle weakness, slurred speech, blurred vision, mouth droop, and/or eyelid droop." Id.

One month after Mr. Smilo received his flu vaccination, he was seen by Dr. Floyd in the office on November 17, 2016. Pet. Ex. 62 at 1-2. Dr. Gavin noted Dr. Floyd "[was] no longer with [the] practice group." Id. at 2. Dr. Gavin provided a summary of the record from this office visit in his affidavit. Id. Included in this part of the affidavit is a quote from Dr. Floyd's note stating, "right eye droop [three] months." Id. (emphasis omitted).

Based on the content of the affidavit, it does not appear that Dr. Gavin saw Mr. Smilo when he presented to the office on November 17, 2016. See Pet. Ex. 62 at 2. Dr. Gavin reiterated, however, that Mr. Smilo had no prior complains of dysphagia or trouble swallowing. Id. at 2. Based on his review of Dr. Floyd's medical record, as well as his review of his own prior records, Dr. Gavin opined that Mr. Smilo's "onset of [] tightness in throat, eye drooping, slurred speech, and right side mouth droop was within one [] week or one []day[] of his November 17, 2016 office visit." Id. He further opined that Dr. Floyd's "medical entry of 'droopy eye for [three] months' is erroneous." Id. at 3.

In Dr. Gavin's August 22, 2016 record, he noted Mr. Smilo recently saw Dr. Ives, his optometrist, and "Mr. Smilo made no mention that the optometrist found ptosis of his eye nor did [Dr. Gavin] observe any ptosis." Pet. Ex. 62 at 2. Dr. Gavin also reviewed the records of Dr.

Mejia, another physician in the practice, and according to Dr. Gavin, there was no reference to ptosis in those records. Id.

C. Expert Reports

1. Petitioner's Expert, Dr. George A. Small[22]

a. Background and Qualifications

Dr. Small is a board-certified neurologist and neuromuscular specialist. Pet. Ex. 10 at 1; Pet. Ex. 11 at 3. After obtaining his M.D. from Jefferson Medical School in Philadelphia, Pennsylvania, he completed an internal medicine internship, neurology residency, and clinical neuromuscular disease and electromyography ("EMG") fellowship. Pet. Ex. 11 at 1. Over the course of his career, he has held various teaching and hospital positions as well as membership and appointments to professional societies and committees, and has authored or co-authored over 40 publications. Id. at 2, 4-9. Dr. Small is also "a board member of the Myasthenia Gravis Association of Western Pennsylvania and ha[s] extensive experience in the diagnosis and management of patients with [m]yasthenia [g]ravis." Pet. Ex. 10 at 1.

b. Opinion

Dr. Small opined that the mechanisms that would explain the development of myasthenia gravis were "an autoimmune reaction to the vaccine by means of molecular mimicry, bystander activation, or polyclonal activation." Pet. Ex. 10 at 4. Of these, he believed that molecular mimicry was "the most probable theory as to why Mr. Smilo developed myasthenia gravis . . . as a consequence of his [flu] vaccine." Pet. Ex. 46 at 2. Although Dr. Small believed that Mr. Smilo did not develop myasthenia gravis until after vaccination, if Mr. Smilo did have myasthenia gravis at the time of his flu vaccination, then "within a reasonable degree of medical and scientific certainty," Mr. Smilo's myasthenia gravis was "significantly aggravated" due to his vaccination "by reason of the same pathologic autoimmune processes." Pet. Ex. 10 at 6.

i. Loving Factor Four/Althen Prong One

According to Dr. Small, molecular mimicry is "[t]he most common mechanism by which infections or vaccines induce autoimmunity." Pet. Ex. 10 at 4 (quoting Pet. Ex. 13 at 2).[23] Molecular mimicry is the process whereby an infection or vaccine "incorporates an epitope that is structurally similar to a self-antigen and therefore induces self-reactivity." Id. (quoting Pet. Ex. 13 at 2).

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[22] Petitioner submitted two expert reports from Dr. Small. Pet. Exs. 10, 46.

[23] Nancy Agmon-Levin et al., Influenza Vaccine and Autoimmunity, 11 Isr. Med. Ass'n J. 183 (2009).

In support of the theory of molecular mimicry, Dr. Small cited an article by Wucherpfennig[24] that described the mechanisms by which infectious agents cause autoimmune illnesses. Pet. Ex. 43. Wucherpfennig defined molecular mimicry as the mechanism whereby "[p]eptides from microbial proteins that have sufficient structural similarity with self-peptides can activate autoreactive T cells." Id. at 1. Wucherpfennig provided examples of molecular mimicry, including experimental autoimmune encephalitis ("EAE"), where a peptide sequence from a hepatitis B virus was identical to six amino acids of myelin basic protein in rabbits. Id. at 2. Wucherpfennig, however, did not discuss vaccines or myasthenia gravis.

Dr. Small agreed with Petitioner's other expert, Dr. DeAngelo, whose opinions are discussed below, that molecular mimicry was the most likely theory to explain Mr. Smilo's development of myasthenia gravis after vaccination. Pet. Ex. 46 at 2. Dr. Small opined that the flu vaccination initiated

> a complex interaction of T cells which reacted to the presence of the exogenously administered [flu] proteins, caused production of antibodies that both would attack the [flu] virus itself and also cause an apparent formation of [AChR] antibodies, which are the specific proteins response for decreasing the ability of motor nerves to activate muscles, thereby causing muscle weakness and dysfunction.

Id. "[T]he antibodies produced in response to the vaccine antigen mistakenly bind to the postsynaptic region and impair the function of the [AChR]. Simply put, with fewer receptor sites available, the muscles receive fewer nerve signals, resulting in weakness and clinical manifestation of the disease." Pet. Ex. 10 at 4.

Dr. Small cited several articles specific to vaccines that he asserted demonstrate that "the [flu] vaccine may trigger or exacerbate the symptoms of autoimmune neurological diseases such as Guillain-Barre syndrome, [acute disseminated encephalomyelitis], transverse myelitis, and systemic lupus erythematosus." Pet. Ex. 10 at 3. The first of these, by Agmon-Levin et al., did not discuss myasthenia gravis or any other neuromuscular autoimmune illness. See Pet. Ex. 13. The authors discussed adjuvants, which are sometimes "added to vaccines to improve their immunogenicity." Id. at 2. There is no evidence here, however, that the flu vaccine given to Mr. Smilo contained an adjuvant.

The next article cited by Dr. Small was from Domigo et al.,[25] and in it, the authors questioned whether the hepatitis B vaccine should be administered to those with myasthenia

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[24] Kai W. Wucherpfennig, Mechanisms for the Induction of Autoimmunity by Infectious Agents, 108 J. Clinical Investigation 1097 (2001). Petitioner's other expert, Dr. DeAngelo, also discussed this article. See Pet. Ex. 18 at 6-8, 14.

[25] Valérie Domigo et al., Should Hepatitis B Vaccine Be Contra-indicated in Myasthenia Gravis?, 29 Autoimmunity 139 (1998). Dr. DeAngelo also cited this article. Pet. Ex. 69.

gravis.[26] Pet. Ex. 14 at 1. The authors provided case reports on two patients. Id. The first patient had no prior history of symptoms and developed neuromuscular symptoms one week after a plasma-derived hepatitis B vaccine. Id. The second patient had a prior diagnosis of myasthenia gravis, and her condition worsened in the month following her second injection of the hepatitis B vaccine. Id. These cases did not involve the flu vaccine.

The last article cited by Dr. Small, from Sanghani et al.,[27] reported a study utilizing VAERS data about post-vaccination cases of myasthenia gravis. Pet. Ex. 15. Unfortunately, only the abstract was filed, and therefore, the information was limited. See id. The authors reviewed 71 reports of adult cases of myasthenia gravis from 1990 to 2017. Id. at 2. Of these, 73.6% were "newly diagnosed," with an onset within six weeks of vaccination in the majority of cases (77%). Id. The two most reported preceding vaccines were flu (26 cases or 36%) and hepatitis B (17 cases or 24%). Id. The authors concluded that their "results suggest that the reporting rate of post vaccination [myasthenia gravis] overlaps with its incidence in the general population." Id. The authors also postulated that because most cases occurred within six weeks of vaccination, "some [] could be triggered by vaccination." Id. The undersigned finds these conclusions confusing because the authors stated that the incidence of myasthenia gravis after vaccination is the same as that in the background population, suggesting that there is no increased incidence attributable to vaccination. See id. However, the authors also suggested that the temporal association between vaccination and onset of myasthenia gravis suggests a potential causal association. See id. Without complete data, the information in this abstract and the authors' conclusions are difficult to understand.

ii. Loving Factor Five/Althen Prong Two

Dr. Small opined that "to [a] reasonable degree of medical and scientific certainty[,] [] the [flu] vaccination Mr. Smilo received on October 17, 2016 did cause his myasthenia gravis disease." Pet. Ex. 10 at 4. He opined that Mr. Smilo experienced an autoimmune illness, and that literature and studies have associated myasthenia gravis with vaccines, including the flu vaccination. Id. at 4-5.

Prior to vaccination, Dr. Small explained that Mr. Smilo was "relatively healthy." Pet. Ex. 10 at 5. Diagnostic studies were done, and there was no other cause found for Mr. Smilo's myasthenia gravis. Id. Further, Dr. Small averred that there was no other "explainable antigen" except vaccination. Id. Additionally, Dr. Smilo noted that "Mr. Smilo's primary care physician, Dr. Gavin, filed a VAERS report noting the post-[flu] vaccine myasthenia gravis sequela." Id.

Further, Dr. Small opined that myasthenia gravis and its resulting complications significantly contributed to Mr. Smilo's death. Pet. Ex. 10 at 5-6. Due to difficulty swallowing,

[26] Of note, the article was published in 1998, and therefore, it may not reflect the most current information.

[27] Nirav Sanghani et al., Myasthenia Gravis After Vaccination in Adults the United States: A Report from the CDC/FDA Vaccine Adverse Event Reporting System (1990-2017), 90 Neurology 6.437 (2018). Dr. DeAngelo also cited to this abstract. Pet. Exs. 60, 73.

Mr. Smilo was unable to eat, causing a weight loss of 70 pounds and requiring a PEG tube. Id. at 5. According to Dr. Small, this led to a "very weakened and debilitated general state" and made him more vulnerable to "co-existent disease." Id. at 6. Due to his myasthenia gravis, Mr. Smilo experienced a "rapid and pronounced decline in his overall health," which was "a significant contributing factor in bringing about his death." Id.

In summary, Dr. Small believed that "Mr. Smilo had a vaccine-induced autoimmune event resulting in the onset of his myasthenia gravis." Pet. Ex. 10 at 5. "[I]n the absence of other possible infectious and noninfectious etiologies, of which none was identified in his work-up and examination, the diagnosis of post-vaccination myasthenia gravis is most probable." Id. Moreover, Dr. Small opined that Mr. Smilo's myasthenia gravis was a significant factor in his death. Id. at 5-6.

iii. Loving Factor Six/Althen Prong Three

Regarding onset, Dr. Small opined that Mr. Smilo developed symptoms of myasthenia gravis approximately three weeks after vaccination. Pet. Ex. 10 at 4-5. He explained that a three-week interval between vaccination and onset was an appropriate time frame within which the immune-mediated mechanism could occur, resulting in the autoimmune manifestations consistent with myasthenia gravis. Id.

While Dr. Small acknowledged that there were references in the medical records about Mr. Smilo having an eye droop that predated his flu vaccination, Dr. Small noted that Mr. Smilo was not diagnosed with myasthenia gravis prior to vaccination. Pet. Ex. 10 at 6. Further, Dr. Small asserted that Mr. Smilo did not have "any other symptoms of myasthenia gravis such as dysphagia, dysarthria, muscle weakness, or respiratory distress." Id. Dr. Small surmised that the "eye droop could have resulted from an unrelated muscle deficiency specific to that eye muscle as opposed to a larger neuromuscular disease process." Id.

In support of his opinion that Mr. Smilo did not have ptosis prior to vaccination, Dr. Small referred to the optometry records of Dr. Ives dated October 19, 2016, which did not document that Mr. Smilo had ptosis. Pet. Ex. 46 at 1. Dr. Ives' records documented that Mr. Smilo had cataracts and glaucoma, which suggested to Dr. Small that if ptosis had been present before the date of vaccination, Dr. Ives would have documented it. Id. at 1-2. Thus, Dr. Small opined that "it is reasonable to conclude" that Mr. Smilo did not have ptosis at the time of the visit, or prior to vaccination on October 17, 2016. Id. at 2.

As for Mr. Smilo's symptom of difficulty swallowing, Dr. Small attributed it to his esophageal reflux that was present prior to vaccination. Pet. Ex. 46 at 2. Dr. Small also observed that Mr. Smilo's records did not document that he had ptosis or difficulty swallowing on the date that he received his vaccination, October 17, 2016. Id. Dr. Small asserted that this fact further supports his opinion that Mr. Smilo did not have myasthenia gravis on the date of vaccination. Id.

Although Dr. Small did not believe that Mr. Smilo had myasthenia gravis at the time of vaccination, he opined that if Mr. Smilo did have myasthenia gravis, then "within a reasonable

degree of medical and scientific certainty[,] [Mr. Smilo's myasthenia gravis] was significantly aggravated as a result of said vaccination by reason of the same pathologic autoimmune processes." Pet. Ex. 10 at 6.

2. Petitioner's Expert, Dr. James N. DeAngelo[28]

a. Background and Qualifications

Dr. DeAngelo is a board-certified allergist and immunologist. Pet. Ex. 18 at 2; Pet. Ex. 44 at 2. He obtained his D.O. from the Philadelphia College of Osteopathic Medicine, after which he completed an internship in family medicine, a residency in internal medicine, and a fellowship in allergy and immunology. Pet. Ex. 44 at 1. For over 20 years, he has worked at Allergy and Clinical Immunology Associates. Pet. Ex. 18 at 2. He is also active in teaching and clinical research. Id.; Pet. Ex. 44 at 3-17.

b. Opinion

Dr. Angelo opined that "within a reasonable degree of medical and scientific probability," Mr. Smilo suffered "myasthenia gravis [] from the [flu] vaccine" that he received on October 17, 2016. Pet. Ex. 18 at 1. He also believed that because Mr. Smilo developed myasthenia gravis as a result of vaccination, he "required immunosuppressive treatment with azathioprine," and this medication caused his death from HCC. Id.

i. Loving Factor Four/Althen Prong One

The mechanism of causation proposed by Dr. DeAngelo is an "immune-mediated haptenation[29] theory; that is, the process by which a foreign small-molecule hapten conjugated to a self-protein creates a 'neo-antigen,' capable of inducing autoimmunity" via molecular mimicry and/or bystander activation. Pet. Ex. 63 at 1, 3-4. Over his four reports, Dr. DeAngelo refined his theory in the context of post-vaccination myasthenia gravis. He started with general principles of molecular mimicry, and then developed his theory of haptenization. Dr. DeAngelo also referenced additional concepts or mechanisms, including neo-antigens, bystander activation, superantigens, and polyclonal activation. Additionally, he provided medical literature and case reports.

1. Molecular Mimicry

In his first report, Dr. DeAngelo described molecular mimicry as the process by which "inflammation from viral antigens in the vaccine results in local activation of antigen-presenting cells that, in turn, results in enhanced processing and presentation of self-antigens." Pet. Ex. 18 at 6. He asserted that molecular mimicry is "the most widely accepted hypothesis as to how viral vaccine antigens produce and maintain autoimmune responses." Id. at 7. As an example, Dr.

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[28] Petitioner submitted four expert reports from Dr. DeAngelo. Pet. Exs. 18, 47, 55, 63.

[29] Dr. DeAngelo also referred to this as "haptenization." See Pet. Ex. 63 at 2.

DeAngelo explained how *Streptococcus pyogenes*, the bacteria that causes strep throat, can cause autoimmune complications including rheumatic fever and glomerulonephritis. Id. at 8-9.

According to Dr. DeAngelo, molecular mimicry is either T-cell dependent or T-cell independent. Pet. Ex. 18 at 7. In the T-cell mediated form, "autoreactive T cells are activated by peptides" with "structural similarity to self-peptides," and these reactive T cells (lymphocytes) "recognize fragmentized microbial peptide antigens presented by major histocompatibility complex (MHC) I or II glycoprotein molecules on antigen-presenting cells." Id. Autoreactive antibodies are generated and attach to the cell surface of a "antigenically similar peptide sequence" or "attach directly to cross-reactive self-antigens, initiating a cascade of autoimmune damage to the host tissue." Id. at 8.

After vaccination, the "immune system [] produce[s] antibodies that recognize and bind to viral hemagglutinin (HA) and neuraminidase (NA) surface proteins. Antibody and T-cell binding to these antigenic sites is necessary for antibodies [to] neutraliz[e] [] the virus and [] prevent[] or mitigate[e] [] the illness." Pet. Ex. 47 at 3. Dr. DeAngelo explained that the flu virus mutates every year, resulting in "variations in these surface antigen proteins, and less commonly, in major antigenic shifts from one HA or NA to another." Id. These changes require the flu vaccine to be changed every year to "antigenically match" the "antigenic character" of the virus. Id. Dr. DeAngelo opined that "these surface proteins are the cause of Mr. Smilo's idiosyncratic autoimmune reaction to the [flu] vaccine." Id. He attributed this "antigenic variability" in the flu vaccine from year to year as the reason that studies have not found "a convincing relationship between [the] [flu] vaccination" and myasthenia gravis.[30] Id. Regardless, he opined that "it is undoubtedly possible that a similarly rare and challenging to prove association exists between the [flu] vaccine and Mr. Smilo's [myasthenia gravis]." Id. at 4.

Specific to myasthenia gravis, although not in the context of vaccination, Dr. DeAngelo cited research by Schwimmbeck et al.[31] to support the mechanism of molecular mimicry as playing a causal role in myasthenia gravis. Pet. Ex. 36. Schwimmbeck et al. reported a homologous protein sequence shown to cross-react between an AChR epitope and a herpes simplex virus glycoprotein. Id. at 1. The authors suggested that the herpes simplex virus may be associated with some cases of myasthenia gravis. Id.

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[30] For support, Dr. DeAngelo cited to an article authored by Zinman et al., cited by Respondent's expert, Dr. Lancaster, and discussed below, which did not find any association between the flu vaccination and myasthenia gravis. Pet. Ex. 47 at 3 (citing Resp. Ex. A, Tab 4 (Lorne Zinman et al., Safety of Influenza Vaccination in Patients with Myasthenia Gravis: A Population-Based Study, 40 Muscle & Nerve 947 (2009)).

[31] P L Schwimmbeck et al., Molecular Mimicry and Myasthenia Gravis: An Autoantigenic Site of the Acetylcholine Receptor Alpha-Subunit That Has Biologic Activity and Reacts Immunochemically with Herpes Simplex Virus, 84 J. Clinical Investigation 1174 (1989).

Dr. DeAngelo also cited a paper by Stübgen.[32] Pet. Ex. 39. Stübgen examined the relationship between the hepatitis B vaccination and myasthenia gravis, and reported that "onset or exacerbation of myasthenia gravis [] was very rarely associated with the [hepatitis B] vaccine." Id. at 3. Further, Stübgen opined that hepatitis B causation "appeared temporal only; a molecular mimicry relationship seemed unlikely" because the potential mimics were "structurally unrelated." Id. While Stübgen suggested it was "conceivabl[e]" that the hepatitis B vaccine provoked myasthenia gravis, Stübgen did not opine that vaccine causation was likely. Id.

The next paper cited by Dr. DeAngelo in support of molecular mimicry was from He et al.,[33] where mice injected with a live-attenuated Japanese encephalitis vaccine developed significant antibodies and some features of myasthenia gravis. Pet. Ex. 26 at 3-4, 8. The mice were also given other vaccines, including hepatitis B, diphtheria-tetanus-pertussis, measles-mumps-rubella, and Bacillus Calmette-Guérin ("BCG"), however, these vaccinations did not induce muscular weakness characteristic of myasthenia gravis. Id. at 3, 7 fig.2, 8, 13.

Lastly, Dr. DeAngelo cited Im et al.,[34] who reported on a study where rats were injected with *Haemophilus influenzae*[35] with a "mimicry peptide" that was "50% homologous" to a T-cell epitope of AChR α subunit. Pet. Ex. 29 at 6. Interestingly, instead of inducing disease, the result was "protection against subsequent induction of [experimental autoimmune myasthenia gravis]," demonstrating that "a microbial-derived peptide can modulate the antibody-mediated auto-immune response in [experimental autoimmune myasthenia gravis]." Id. at 7. The authors suggested that "in some cases[,] cross-reactive microbial proteins and peptides derived from viruses or bacteria can work as protective immunomodulators in regulation of T-cell-mediated autoimmune disease." Id. at 6.

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[32] Joerg-Patrick Stübgen, Neuromuscular Disorders Associated with Hepatitis B Vaccination, 292 J. Neurological Scis. 1 (2010).

[33] Dan He et al., Molecular and Clinical Relationship Between Live-Attenuated Japanese Encephalitis Vaccination and Childhood Onset Myasthenia Gravis, 84 Annals Neurology 386 (2018).

[34] Sin-Hyoeg Im et al., Protective Molecular Mimicry in Experimental Myasthenia Gravis, 126 J. Neuroimmunology 99 (2002).

[35] *Haemophilus influenzae* is "a species once thought to be the cause of epidemic [flu]." Haemophilus Influenzae, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=79896 (last visited Apr. 24, 2023).

Dr. DeAngelo conceded that Tackenberg et al.[36] did not find that the flu vaccine caused or exacerbated myasthenia gravis; however, he attributed the outcome to the small study size. Pet. Ex. 18 at 12 (citing Pet. Ex. 40 at 1). The study included 62 patients with myasthenia gravis (with known antibodies against AChR), randomized to receive either the seasonal flu vaccine (31 patients) or a placebo (31 patients). Pet. Ex. 1-2. Baseline AChR antibody titers were compared to values at three and 121 weeks post-vaccination. Id. at 2. There were no cases of "clinical deterioration nor any serious or severe adverse events due to vaccination." Id. at 3. Further, there was no "clinically relevant increase of AChR-[antibody]-titer," no increase in aggravation of myasthenia gravis, and no increase in adverse events. Id. at 5.

2. Haptenization

In his second expert report, Dr. DeAngelo introduced the concept of haptenization. Pet. Ex. 47 at 4. He stated that "[t]he introduction of any foreign material to the human body always raises the possibility of haptenization." Id. "According to the classic hapten theory, . . . the immune reaction to molecularly small, normally non-antigenic compounds, known as haptens, results from the hapten binding with a carrier protein from the patient to generate an autoimmune response." Id. at 4-5. "Haptenization is now a well-established mechanism whereby a non-immunogenic drug or vaccine is rendered immunogenic via molecular mimicry." Id. at 5.

In support of his haptenization/molecular mimicry mechanism, Dr. DeAngelo cited an article by Bugelski.[37] Pet. Ex. 49. Bugelski explained that "[m]ost small-molecule drugs or xenobiotics (that is, non-peptides with a molecular mass of ~300-600 Da) are not direct immunogens." Id. at 1. For there to be "immunogenicity," there must be a "covalent conjugation of the xenobiotic to a host protein." Id. at 2. An example is penicillin, which can trigger a severe immune reaction (anaphylactic reaction), probably through "the formation of [a] drug-protein conjugate[]." Id. Bugelski explained that "[t]he formation of hapten-peptide conjugates is [] the first step in the activation of the immune system." Id. The hapten-peptide conjugate is "carried to and displayed—in conjugation with major histocompatibility complex (MHC) proteins, . . . also known as human lymphocyte antigen (HLA) proteins—on the surface of antigen-presenting cells (APCs)." Id. The "[h]apten-peptide conjugates on the surface of APCs interact with immature T and B lymphocytes through T- and B-cell receptors, respectively." Id. The immune system is then activated, and "governed by the antigen-binding specificity of the T- and B-cell receptors." Id. Thus, through the complex process described by Bugelski, some hapten-peptide conjugates may play a role in activating the immune system. See id. These immune-mediated adverse drug effects are "the result of complex interactions between

[36] Björn Tackenberg et al., Acetylcholine Receptor Antibody Titers and Clinical Course After Influenza Vaccination in Patients with Myasthenia Gravis: A Double-Blind Randomized Controlled Trial (ProPATIent-Trial), 28 EBioMedicine 143 (2018). Dr. Lancaster also cited this article. Resp. Ex. A, Tab 3.

[37] Peter J. Bugelski, Genetic Aspects of Immune-Medicated Adverse Drug Effects, 4 Nature Revs. 59 (2005).

drug-metabolizing enzymes, immune sensitization[,] and immune effectors," along with "genetic aspects of this interplay."[38] Id. at 1.

Dr. DeAngelo took Bugelski's explanation about how drug haptens are formed from non-immunogenic molecules, and co-opted it to posit that the flu vaccine could produce "autoreactive immunoglobulin G (IgG) [],[39] specific to the AChR." Pet. Ex. 47 at 6 fig.1, 7 fig.2. In doing so, Dr. DeAngelo altered two figures from Bugelski by changing words in the figures and in the paragraphs describing the figures, and then reached conclusions that were not discussed by Bugelski. Compare id., with Pet. Ex. 49 at 3 fig.1, 5 fig.2.

In summary, Bugelski discussed how xenobiotics, small molecules that do not cause an immune response, can become linked to a protein, and through a complex process, and with the interaction of metabolic enzymes, can ultimately cause an immune response. See Pet. Ex. 49 at 1-2. The concepts are taken out of context, and Dr. DeAngelo cited no precedent for their application in the context of the facts and circumstances here. Further, Bugelski did not describe how vaccines generally, or the flu vaccine specifically, could, through haptenization-induced molecular mimicry, create an immune response that could lead to the development of myasthenia gravis.

3. Neo-antigen and Hapten-Modified Cancer Vaccines

In his fourth and final expert report, Dr. DeAngelo introduced the concept of a neo-antigen as part of his hapten theory—"that is, the process by which a foreign small-molecule hapten conjugated to a self-protein creates a 'neo-antigen' capable of inducing autoimmunity." Pet. Ex. 63 at 1. The concept of the neo-antigen is his response to Respondent's expert's, Dr. Lancaster's, criticism of his theory. Id. Dr. DeAngelo offered his hapten/molecular mimicry/neo-antigen theory to explain how a "strong 3-dimensional molecular homology with human skeletal muscle [AChR] can occur." Id. According to Dr. DeAngelo, "[t]he process of haptenation creates a neo-antigen . . . one that is new and not previously present." Id. at 2. The process of haptenation "is a well-recognized mechanism of autoimmune disease initiation and breakdown of self-tolerance." Id. Further, "haptenation of an endogenous self-protein contorts the three-dimensional conformation for self-proteins, exposing previously hidden epitopes and rendering them immunogenic." Id. Dr. DeAngelo acknowledged that the "application of the haptenation theory to induce or exacerbate autoimmunity is somewhat novel in the context of the presentation of post-vaccine myasthenia gravis," but argued that nonetheless, it is "sound and reliable." Id. at 1.

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[38] For the complete description of this process, see Pet. Ex. 49 at 2-4.

[39] Immunoglobulins are "structurally related glycoproteins that function as antibodies." Immunoglobulin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24894 (last visited Apr. 24, 2023). For more information on IgG, see Peter J. Delves, Acquired Immunity, Merck Manual, https://www.merckmanuals.com/home/immune-disorders/biology-of-the-immune-system/acquired-immunity# (last updated Sept. 2022).

In support of these ideas, Dr. DeAngelo cited to Bolon,[40] who described the loss of self-tolerance, and its role in the development of autoimmune disease:

> Under normal conditions, the immune system exhibits tolerance (an inability to react) to molecules recognized as "self," and thus does not respond to elements (whether carbohydrate, nucleic acid, or protein) that are expressed in endogenous tissues. When self-tolerance is lost, the immune system is deployed against one or more of the body's own molecules.

Pet. Ex. 66 at 1. Bolon described "recent themes" relevant to "pathogenic mechanisms that lead to the end of self-tolerance." Id. One mechanism for the breakdown of self-tolerance was "[s]elf-antigen alteration by attachment of a hapten (chemical or metal) to make a neo-antigen." Id. at 4 tbl.2.

Bolon further explained that the formation of a neo-antigen is a "primary means" of autoimmune disease induction. Pet. Ex. 66 at 9.

> The conjugation of a hapten—usually a reactive metal or small chemical—to an endogenous molecule changes the self-epitope's confirmation. Contortions in the cross-linked molecule generally will expose new epitopes, when may be recognized as new antigens. Alternatively, the conjugated endogenous molecule may now have a much higher affinity for MHC II, which will process it to reactivate anergic cells. Any resulting [autoimmune disease] stemming from production of an immune response against a neo-antigen may persist after the hapten is cleared, presumably because the reaction is manly against the endogenous portion of the complex.

Id. (internal citations omitted). As described by Bolon, the conjugation of a hapten usually involves a reactive metal or small chemical, not a vaccine, and not the flu vaccine. See id.

Dr. DeAngelo also referenced two articles by Berd related to the development of anticancer vaccines, not vaccines used to prevent infectious illness, like the flu vaccine, in support of his theory. See Pet. Ex. 64;[41] Pet. Ex. 65.[42] In the first, Berd discussed hapten-modified tumor vaccines. Pet. Ex. 64 at 1. He began by describing the discovery of haptens, "simple chemicals . . . incapable of inducing an immune response by themselves, but [] immunogenic when attached . . . to a protein carrier." Id. Six haptens have been studied and

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[40] Brad Bolon, Cellular and Molecular Mechanisms of Autoimmune Disease, 40 Toxicologic Pathology 216 (2012).

[41] David Berd, Hapten-Modified Tumor Vaccines, in Handbook of Cancer Vaccines 275 (Michael A. Morse et al. eds., 2004).

[42] David Berd et al., Immunopharmacologic Analysis of an Autologous, Hapten-Modified Human Melanoma Vaccine, 22 J. Clinical Oncology 403 (2004).

used in research for their various immunological responses. Id. at 3 tbl.1. Berd explained that hapten conjugation has been used to provide "new antigenic determinants" to "increase the binding of T-cell receptors (TCRs) to self peptide enough for T-cell activation, and once activated, the T cells could react with unmodified peptide." Id. at 4. In more simple terms, haptens can be used to modify "otherwise nonimmunogenic peptide[s]" to induce an immune response. Id. For example, mice injected with "hapten-modified thyroglobulin developed histological evidence of autoimmune thyroiditis." Id. These concepts have been applied in the context of immunotherapy for treatment of cancer (hapten immunology); hapten-modified vaccines have been developed for animal experiments with the goal of treating aggressive tumors. Id. at 5-7. "[H]apten modification can result in immune responses" that can be applied to "tumor antigens" to delay or slow tumor growth. Id. at 19. Berd, however, did not discuss how haptens could be relevant to the facts and circumstances here, or explain how a flu vaccine could cause myasthenia gravis. The same is true for the second article by Berd et al., which also described a hapten-modified human melanoma vaccine. See Pet. Ex. 65.

In summary, Dr. DeAngelo has suggested that hapten conjugation in the context of vaccination can somehow be involved in the pathogenesis of myasthenia gravis, but the articles cited do not explain how vaccines given to protect against viral infection, or the flu vaccine specifically, can cause myasthenia gravis. See Pet. Ex. 63 at 1-3.

4. Bystander Activation

In addition to molecular mimicry, Dr. DeAngelo stated that "[o]nce autoimmunity is initiated via hapten-generated molecular mimicry, downstream T-cell Th1, Th2, Th17, and B cell effectors induce cytokine, cytotoxic cellular, and autoantibody responses to not only the hapten and hapten-carrier complex but also previously tolerated self-peptides." Pet. Ex. 63 at 3. This downstream activity "can result in a generalized pro-inflammatory environment, whereby 'bystander activation' occurs." Id. Dr. DeAngelo defined "bystander activation" as "the nonspecific activation of previously quiescent immune cell lines." Id.

Dr. DeAngelo suggested that bystander activation "is of particular interest," assuming Mr. Smilo had myasthenia gravis prior to vaccination. Pet. Ex. 63 at 3. In that scenario, Dr. DeAngelo stated that "hapten-generated molecular mimicry [is] less critical" because "[AChR] autoantibody generation may have already been underway." Id. Regardless, he opined that bystander activation "could increase autoantibody generation, enhance T-cell cytotoxicity, amplify the existing inflammatory cytokine milieu, increase the upregulation of the immune system, and thereby exacerbate [Mr. Smilo's] underlying autoimmune disease and its resulting symptomology." Id.

5. Superantigens, Polyclonal Activation, and Epitope Spreading

Other ideas offered by Dr. DeAngelo involve "superantigens"[43] and "polyclonal activation." Pet. Ex. 63 at 3. He stated that "under certain circumstances, where a superantigen is generated by the hapten complex, polyclonal activation takes place." Id. Citing Bolon, he defined polyclonal activation as "the process whereby superantigen[s] drive[] nonspecific cross-linking of MHC II to TCR on numerous T-cell lineages [that] results in them becoming primed for myriad epitopes. Such epitopes are involved in the original hapten-mediated loss of tolerance, but their unintended activation releases even more cytokines." Id. (citing Pet. Ex. 66 at 3-4). Bolon, however, does not discuss superantigens or this mechanism. And Dr. DeAngelo does not define superantigens or otherwise develop this mechanism.

Next, Dr. DeAngelo identified "polyclonal activation of memory B-cells" as a "contributing immunologic driver" of Mr. Smilo's myasthenia gravis. Pet. Ex. 18 at 14. He cited Bernasconi et al.,[44] who "show[ed] that human memory B lymphocytes proliferate and differentiate into plasma cells in response to polyclonal stimuli, such as bystander T cell help[ers]." Pet. Ex. 20 at 1. But Dr. DeAngelo did not explain how this process applies in the context of alleged post-vaccination myasthenia gravis. See Pet. Ex. 18 at 6-7, 14. And the authors of Bernasconi et al. did not discuss how polyclonal activation of memory B-cells could cause an autoimmune disease due to vaccination, or how vaccination could serve as a "continuing immunologic driver" of illness.

Dr. DeAngelo also suggested that "epitope spreading" may also be a "contributing immunologic driver" of myasthenia gravis. Pet. Ex. 18 at 14. He cited two articles in support of this idea. The first is by Lehmann et al.[45] and dealt with EAE, "a prototype of CD4+ T-cell mediated autoimmune disease" and multiple sclerosis. Pet. Ex. 31 at 1. Dr. DeAngelo did not define "epitope spreading" or explain why he referenced the article.

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[43] Superantigen is "any of a group of powerful antigens occurring in various bacteria and viruses that binds outside of the normal T-cell receptor site and is able to react with multiple T-cell receptor molecules of a given β-chain variable element, regardless of their α-chain sequence, thus activating T cells nonspecifically. Included are staphylococcal enterotoxins and toxins causing toxic shock syndrome and exfoliative dermatitis." Superantigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=48059 (last visited Apr. 24, 2023).

[44] Nadia L. Bernasconi et al., Maintenance of Serological Memory by Polyclonal Activation of Human Memory B Cells, 298 Science 2199 (2002).

[45] Paul V. Lehmann et al., Spreading of T-Cell Autoimmunity to Cryptic Determinants of an Autoantigen, 358 Nature 155 (1992).

The second article is by Smatti et al.[46] and discussed the potential of viruses to modify autoimmune illnesses like diabetes, systemic lupus erythematosus, and others. Pet. Ex. 38 at 1. In the article, "epitope spreading" is defined as the mechanism by which "a viral infection triggers the release of more self-antigens and the de novo activation of autoreactive cells, which consequently spread to target additional self-epitopes." Id. at 2. The authors stated that molecular mimicry and bystander activation have been associated with EAE and multiple sclerosis, West Nile virus-mediated myasthenia gravis, and other illnesses, and provided a review of potential mechanisms of causation, including molecular mimicry, bystander activation, and epitope spreading. Id. at 1-2, 2 fig.1. In the "[e]pitope spreading model," the process begins with "[p]ersistent viral infection," which leads to sustained tissue damage and "release of new self-antigens" and ultimately to autoimmunity. Id. at 2 fig.1. The authors discussed enteric infections, Coxsackie B viruses, rotaviruses, the flu A virus, herpesviruses, and other viruses, as well as the different mechanisms that trigger autoimmune illnesses. Id. at 2-10, 8-10 tbl.1. Myasthenia gravis was identified as an autoimmune disease that has been associated with the West Nile virus and molecular mimicry was identified as the proposed mechanism. Id. at 9 tbl.1. The authors, however, did not discuss vaccines in association with myasthenia gravis, and it is not clear why Dr. DeAngelo cited the article in reference to "epitope spreading." See Pet. Ex. 18 at 14.

6. Case Reports and Data from VAERS[47]

In addition to articles about his various theories, Dr. DeAngelo also referenced case reports in support of his opinions about causation. Chung et al.[48] reported a case of myasthenia gravis with onset three days after administration of the second human papillomavirus ("HPV") vaccination. Pet. Ex. 68 at 1. By week four, the patient's symptoms had "completely resolved." Id. at 2. The authors did not reach any conclusions about this "possible causal relationship." Id. at 3.

Dr. DeAngelo, like Dr. Small, also cited to Domigo et al., who discussed two case reports of myasthenia gravis after the hepatitis B vaccine. Pet. Ex. 14. As explained above, the first patient did not have a history of myasthenia gravis, developed symptoms one week after receipt of a plasma-derived hepatitis B vaccine, and stabilized with treatment. Id. at 1. The second patient had pre-existing myasthenia gravis and her condition worsened after administration of the plasma hepatitis B vaccine. Id. No causal theory was posited by the authors. See id. at 1-2.

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[46] Maria K. Smatti et al., Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms, 11 Viruses 1 (2019).

[47] Dr. DeAngelo also cited a case involving a patient who received intravesical BCG for bladder cancer and developed myasthenia gravis shortly thereafter. Pet. Ex. 75 at 1 (Tsubasa Takizawa et al., New Onset of Myasthenia Gravis After Intravesical Bacillus Calmette-Guerin, 96 Medicine 1 (2017)). Symptoms resolved after treatment with steroids. Id.

[48] Ji Yeon Chung et al., Myasthenia Gravis Following Human Papillomavirus Vaccination: A Case Report, 18 BMC Neurology 1 (2018).

Two cases of myasthenia gravis following Covid-19 vaccines were also cited by Dr. DeAngelo. The first, from Chavez and Pougnier,[49] was an 82-year-old who developed intermittent periods of slurred speech with onset four weeks after receipt of the initial Covid-19 vaccine (and two days after the second dose, but symptoms had preceded the second dose). Pet. Ex. 67 at 1. The patient had elevated AChR antibodies and EMG testing consistent with myasthenia gravis, and had rapid disease progression. Id. at 1-2. The authors discussed the mechanisms of molecular mimicry and bystander activation as related to the mRNA vaccine,[50] and suggested that bystander activation may be the more plausible of the two theories for their patient, noting that "previously existing self-antigen [] released due to stimulation of the innate immune system . . . [may] result[] in activation of auto-reactive T cells." Id. at 2.

The second Covid-19 vaccine case report, authored by Lee et al.,[51] described a 33-year-old who had "generalized weakness and diplopia on the evening she received her second dose" of the vaccine. Pet. Ex. 72 at 1. The patient did not have elevated AChR antibodies and her EMG study was normal. Id. The authors stated that the "underlying pathogenesis [was] unclear," but they suggested that the "changes that take place in the immune response after vaccination could elicit the production of antibodies against [AChR]." Id. at 1.

In addition to case reports, Dr. DeAngelo cited two abstracts of data from the Centers for Disease Control and Prevention ("CDC") and Food and Drug Administration ("FDA"), summarizing reports of myasthenia gravis after vaccinations from VAERS from 1990 to 2017. Pet. Ex. 15 (adult cases);[52] Pet. Ex. 58 (pediatric cases).[53] As previously noted above in Dr. Small's expert report section, 71 adult cases were reported. Pet. Ex. 15 at 2. Of the 71 cases, 57 were determined to be definite cases of myasthenia gravis. Id. The flu and hepatitis B vaccines

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[49] Augustine Chavez & Charlotte Pougnier, A Case of COVID-19 Vaccine Associated New Diagnosis Myasthenia Gravis, 12 J. Primary Care & Cmty. Health 1 (2021).

[50] There is no evidence here that the flu vaccine at issue was an mRNA vaccine. Messenger RNA, or mRNA, are "RNA molecules . . . that serve as templates for protein synthesis (translation); in eukaryotes they have characteristic posttranscriptional modifications, the 5'-cap and poly A tail. The base sequence of an mRNA transcript completely specifies the corresponding polypeptide amino acid sequence." Messenger RNA, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=104391 (last visited Apr. 24, 2023).

[51] Myung Ah Lee et al., Early-Onset Myasthenia Gravis Following COVID-19 Vaccination, 37 J. Korean Med. Sci. 1 (2022).

[52] Both Dr. Small and Dr. DeAngelo cited this abstract. See Pet. Exs. 15, 73.

[53] Rajanigandhi Hanumanthu et al., Pediatric Myasthenia Gravis After Vaccination in the United States: A Report from the CDC/FDA Vaccine Adverse Event Reporting System (1990-2017), 90 Neurology 2.326 (2018).

were most often reported (26 and 17 respectively). Id. Because only an abstract was filed, limited information was provided. The authors concluded that the rate of myasthenia gravis reported was within the expected range based on the general population; however, they recommended monitoring for myasthenia gravis after vaccination due to the temporal association between vaccination and disease onset. Id. No causal mechanisms were discussed. See id.

ii. Loving Factor Five/Althen Prong Two

Dr. DeAngelo opined that "the [flu] vaccine was the most likely cause of Mr. Smilo's [myasthenia gravis]." Pet. Ex. 55 at 4. He stated "[t]here is the potential for the seasonal [flu] vaccine to induce [myasthenia gravis] in the constitutionally predisposed individual via haptenization-induced molecular mimicry." Id.

He summarized that "Mr. Smilo received his [flu] vaccine on October 17, 2016, with his symptoms of [myasthenia gravis] presenting or significantly worsening approximately three [] weeks post-vaccine." Pet. Ex. 63 at 5. Further, Dr. DeAngelo noted that there was no other "inciting causal infectious or noninfectious" cause for Mr. Smilo's illness recorded in his medical records. Id.

Lastly, Dr. DeAngelo observed that Mr. Smilo's primary care physician, Dr. Gavin, "filed a VAERS report identifying a potential causal and temporal relationship between the administration of the [flu] vaccine and his [myasthenia gravis]."[54] Pet. Ex. 63 at 5.

In addition to his opinion that the flu vaccine caused Mr. Smilo's myasthenia gravis, Dr. DeAngelo also opined that "if he had not developed [myasthenia gravis,] . . . he would not have required immunosuppressive treatment with azathioprine and, therefore, may have never died from [HCC]." Pet. Ex. 18 at 1. For this reason, Dr. DeAngelo believed that "Mr. Smilo's [HCC] was likely either induced or accelerated in its progression via treatment with azathioprine." Pet. Ex. 55 at 4. Dr. DeAngelo cited Heron et al.[55] and Fortinsky et al.[56] who noted that azathioprine was associated with HCC in patients with Crohn's disease. Pet. Ex. 27 at 1; Pet. Ex. 24 at 1. Additionally, Dr. DeAngelo noted Buell et al.[57] "report[ed] that azathioprine promotes carcinogenesis independent of its immunosuppressive effects." Pet. Ex. 55 at 2 (citing Pet. Ex. 56 at 4) (internal quotation marks omitted).

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[54] Dr. Gavin's VAERS report does not include an opinion as to a causal association between vaccination and Mr. Smilo's myasthenia gravis. See Pet. Ex. 9.

[55] Valérie Heron et al., Resected Hepatocellular Carcinoma in a Patient with Crohn's Disease on Azathioprine, 10 Case Reps. Gastroenterology 50 (2016).

[56] Kyle J. Fortinsky et al., Metastatic Hepatocellular Carcinoma in a Patient with Crohn's Disease Treated with Azathioprine and Infliximab: A Case Report and Literature Review, 2014 Case Reps. Gastrointestinal Med. 1.

[57] Joseph F. Buell et al., Malignancy After Transplantation, 80 Transplantation S254 (2005).

Thus, like Dr. Small, Dr. DeAngelo opined that Mr. Smilo "may never had developed HCC if he had not been treated with azathioprine" given for treatment of his myasthenia gravis. Pet. Ex. 18 at 15. Hence, Dr. DeAngelo concluded that "the [flu] vaccine was the original precipitating event that lead to Mr. Smilo's eventual decline from [myasthenia gravis] and [] death from a combination of his debilitated state and the advanced HCC." Id.

iii. Loving Factor Six/Althen Prong Three

Regarding the temporal association between vaccination and onset of myasthenia gravis, Dr. DeAngelo opined that "the onset or significant worsening of [Mr. Smilo's] [myasthenia gravis] symptomology did not manifest until approximately three (3) weeks following administration of his [flu] vaccine." Pet. Ex. 63 at 5. According to Dr. DeAngelo, Mr. Smilo received his vaccination on October 17, 2016, and approximately one month after vaccination, he saw Dr. Gavin and complained of a seven-day history of difficulty swallowing and eyelid droop. Pet. Ex. 18 at 3-4.

Dr. DeAngelo further opined that this time frame is consistent with that reported in the case studies of Chavez and Pougnier, Chung et al., and Lee et al., who reported an interval of three days to six weeks between vaccination and onset of myasthenia gravis. Pet. Ex. 63 at 5 (citing Pet. Exs. 67-68, 72). In the case reported by Chung et al, onset was three days after administration of the second HPV vaccination. Pet. Ex. 68 at 1. Three other case reports of myasthenia gravis after HPV and BCG vaccinations were summarized, and onset in those cases ranged from one month to six weeks. Id. at 3 tbl.1. Onset in the two cases of myasthenia gravis following Covid-19 vaccination reported by Chavez and Pougnier and Lee et al. occurred two days after the second dose (four weeks after the initial dose) and on the evening of the second dose, respectively. Pet. Ex. 67 at 1;Pet. Ex. 72 at 1.

In conclusion, Dr. DeAngelo believed that "Mr. Smilo's onset or significant worsening of his [myasthenia gravis] symptomology [was] consistent with the timeframe espoused in the [] medical literature and [] consistent with [his] clinical experience in diagnosing post-infectious autoimmune disease." Pet. Ex. 63 at 5-6.

3. Respondent's Expert, Dr. Eric Lancaster[58]

a. Background and Qualifications

Dr. Lancaster is board-certified in neurology, neuromuscular medicine, and electrodiagnostic studies, "with expertise in antibody-mediated neurological disorders." Resp. Ex. B at 1-2. He obtained a Ph.D. in Neuroscience and an M.D. from the University of Maryland before completing an internship, neurology residency, and neuromuscular fellowships at the University of Pennsylvania. Id. at 1; Resp. Ex. A at 1. Since 2010, he has worked as a neurology professor at the University of Pennsylvania. Resp. Ex. B at 1. Dr. Lancaster has authored over 30 peer-reviewed publications, with his "recent publications mostly concern[ing]

[58] Respondent submitted four expert reports from Dr. Lancaster. Resp. Exs. A, C-E.

autoimmune neurological disorders and their mechanisms." Resp. Ex. A at 1. "[His] clinic is currently focused on autoimmune neurological diseases." Id.

b. Opinion

Dr. Lancaster did not dispute diagnosis, but he disagreed that onset occurred after vaccination and instead opined that Mr. Smilo had symptoms of myasthenia gravis prior to vaccination that "evolved over several months . . . as commonly occurs with myasthenia gravis." Resp. Ex. A at 12-13. Additionally, Dr. Lancaster disputed causation, opining that "[t]here is no reliable evidence that the seasonal [flu] vaccine causes myasthenia gravis." Id. at 8. He explained that "[t]he great majority of myasthenia cases are idiopathic, with a small group triggered by tumors." Id. at 9.

i. Loving Factor Four/Althen Prong One

1. Molecular Mimicry

In response to Petitioner's experts' opinions based on molecular mimicry, Dr. Lancaster noted that Petitioner's experts did not "explain which vaccine constituent would mimic the AchR." Resp. Ex. A at 9, 11. He explained that "molecular mimicry would require a vaccine protein to have a strong 3-diminsinal resemblance to the structure of the human skeletal muscle AchR in order to trigger cross-reactive antibodies." Id. Dr. Lancaster further opined Petitioner's experts "ha[ve] not explained which protein in the vaccine is the mimic nor provided any evidence that such mimicry has ever been reported in any human or animal." Id.

2. Haptenization

Dr. Lancaster opined that there is no evidence that "a hapten effect occurs or that the vaccine produces any immune response to the [AchR]." Resp. Ex. C at 3. Dr. Lancaster explained that the articles cited by Petitioner in support of the hapten theory involve experiments in animals where haptens were injected to illicit immune responses. Resp. Ex. E at 1. For example, he noted the researchers in the Berd papers[59] "create[ed] hapten-modified tumor vaccines by using a known hapten chemical (dinitrophenol) to modify melanoma cells. These cells were injected along with other immune stimulating factors ([BCG]) into patients repeatedly to . . . invoke autoimmunity to the tumor cells" for the purpose of treating cancer. Id. This is very different from the facts and circumstances here, which involves a flu vaccine that is "not designed to become haptenized to any human protein." Id.

Similarly, Dr. Lancaster noted Gefen et al.,[60] cited by Dr. DeAngelo, "d[id] not study or mention myasthenia gravis" or "[flu] vaccination or [flu] proteins." Resp. Ex. D at 3 (citing Pet. Ex. 57). Gefen et al. studied "mice injected with foreign proteins (OVA and BSA) treated with a

[59] See Pet. Exs. 64-65.

[60] Tal Gefen et al., The Effect of Haptens on Protein-Carrier Immunogenicity, 144 Immunology 116 (2015).

series of haptens." Id. (citing Pet. Ex. 57 at 2). Again, Dr. Lancaster concluded that it does not provide any evidence about whether the flu vaccine, or any proteins in it, "can act as haptens to the [AChR]." Id.

While Dr. Lancaster acknowledged that Bugelski generally discussed the process by which haptens are formed, he emphasized that the article did not discuss myasthenia gravis or describe any process by which "a vaccine protein [could] actually act as a hapten in any human autoimmune disease." Resp. Ex. C at 3. In fact, Dr. Lancaster stated this "idea that a vaccine protein could be a hapten has never been demonstrated for any human autoimmune disease." Id.

Breaking down Petitioner's proposed hapten theory into subparts, Dr. Lancaster explained that Dr. DeAngelo posited "that [flu] proteins can act as haptens, that this hapten formation would specifically occur with the [AChR], and that this can actually cause myasthenia gravis." Resp. Ex. C at 3. Because "[t]his is a complex chain of improbable events offered without any supporting evidence," Dr. Lancaster concluded that it is "highly unlikely to be the actual mechanism of [Mr. Smilo's] illness." Id.

3. Bystander Activation and Polyclonal Activation

Although Dr. DeAngelo offered the mechanisms of bystander activation and polyclonal activation, Dr. Lancaster characterized these as "speculative" because Dr. DeAngelo offered no supportive evidence. Resp. Ex. E at 2. Dr. Lancaster agreed that in general, these theories may be relevant in the context of significant aggravation to explain how disease worsens. Id. He explained that "[t]he idea is that [flu] vaccination and the response to [flu] antigens influences cells that already make the antibodies relevant to myasthenia gravis to become more active." Id. However, he asserted that Dr. DeAngelo's discussion of these theories is "vague and general" and with "no specific evidence provided to support this hypothesis." Id.

4. Medical literature[61]

First, Dr. Lancaster addressed the medical literature cited by Petitioner's expert, Dr. Small. As Dr. Lancaster noted, the Agmon-Levin et al. article considered the question of whether the flu vaccine could exacerbate some autoimmune illnesses, like lupus, but the authors did not cite any evidence that the vaccine did worsen lupus. Resp. Ex. A at 8 (citing Pet. Ex. 13). Further, the article did not discuss myasthenia gravis. Id. (citing Pet. Ex. 13). The Domigo et al. article discussed one report of new onset myasthenia gravis and one report of exacerbation of myasthenia gravis following the hepatitis B vaccine; however, Dr. Lancaster noted case reports "represent the lowest level of medical evidence and could represent coincidences." Id. (citing Pet. Ex. 14). Moreover, the flu vaccine was not addressed. Id. (citing Pet. Ex. 14). As for the Sanghani et al. abstract, Dr. Lancaster noted that "the rate of myasthenia [gravis] reported after vaccination was similar to the rate . . . in the general population." Id. (citing Pet. Ex. 15). In addition, he stated that the study design was "less rigorous" than other studies addressing the same issues. Id.

[61] For a list of Dr. Lancaster's criticism of 11 different articles cited by Petitioner, see Resp. Ex. E at 5.

In response to the medical literature discussed by Petitioner's experts, Dr. Lancaster cited three "well-designed [and/or] placebo-controlled studies" confirming the safety of flu vaccinations in patients with myasthenia gravis. Resp. Ex. A at 8-9. Zinman et al. presented a case-series study of 3,667 hospital admissions for myasthenia gravis. Resp. Ex. A, Tab 4 at 1. Of these admissions, there were "513 instances[], [where] hospitalization occurred within 42 weeks following [flu] vaccination in patients previously diagnosed with myasthenia gravis." Id. "Vaccination . . . was not found to be associated with exacerbations of [myasthenia gravis]." Id.

Strijbos et al.[62] conducted a double-blind randomized study in which they administered either a flu vaccine or placebo to 47 patients with myasthenia gravis. Resp. Ex. A, Tab 2 at 1. AChR antibody titers were measured before and after vaccination, and in the vaccination group, they were unchanged after vaccination and did not differ from the non-vaccinated group. Id. There was no exacerbation of myasthenia gravis, even in those patients who were receiving immunosuppressive medications. Id. A similar study was performed by Tackenberg et al. in 62 patients, with half receiving the flu vaccination and the other half receiving a placebo. Pet. Ex. 40 at 1. Vaccination did not increase AChR antibody levels during the observation period of three months and had no adverse effect on the clinical course in the patients with myasthenia gravis. Id. at 6-7.

Next, Dr. Lancaster responded to medical literature cited by Dr. DeAngelo. Resp. Ex. A at 11. As for the Schwimmbeck et al. article reporting cross-reactivity between a human AChR α subunit and herpes simplex virus glycoprotein, Dr. Lancaster observed that the finding has "limited significance" because the herpes simplex virus is "completely different" than the flu virus. Id. (citing Pet. Ex. 36 at 1). Additionally, Dr. Lancaster opined that the mere identification of a potential mimic does not translate to "actual clinical significance." Id. In other words, it is not known whether the herpes simplex virus can "trigger or worsen myasthenia gravis." Id.

Regarding the Stübgen paper, Dr. Lancaster offered similar criticism. Resp. Ex. A at 11. Stübgen studied the hepatitis B virus, not the flu virus. Id. (citing Pet. Ex. 39). Further, Stübgen reviewed medical articles, and therefore, Dr. Lancaster observed that it lacked the "rigor" of Zinman et al., Strijbos et al., or Tackenberg et al. Id. (citing Pet. Exs. 39-40; Resp. Ex. A, Tab 2, 4). Next, He et al. dealt with the Japanese encephalitis vaccine, which Dr. Lancaster pointed out is a different vaccine, and the study was done in a population (China) with "a higher incidence of myasthenia [gravis] . . . compared to other countries," implicating many potential confounders, including "genetics, environment, differences in diagnosis, etc." Id. (citing Pet. Ex. 26). In contrast, Dr. Lancaster explained that the Zinman et al. study was larger and designed to find

[62] Ellen Strijbos et al., A Prospective, Double-Blind, Randomized, Placebo-Controlled Study on the Efficacy and Safety of Influenza Vaccination in Myasthenia Gravis, 37 Vaccine 919 (2019).

more subtle effects of vaccination in myasthenia gravis patients, and the study did not show adverse effects of the flu vaccine in myasthenia gravis patients.[63] Id. at 12.

Dr. Lancaster found Dr. DeAngelo's reference to the abstract by Hanumanthu et al. raised several concerns. Resp. Ex. C at 3 (citing Pet. Ex. 58). As a preliminary issue, Dr. Lancaster searched for the full article but was unable to find anything but an abstract. Id. Dr. Lancaster stated that the abstract presented a summary of reports to VAERS about myasthenia gravis after different vaccinations in children. Id. (citing Pet. Ex. 58). The most common vaccines reported were HPV and hepatitis A/B. Id. (citing Pet. Ex. 58 at 2). They found the incidence of myasthenia gravis was within the range expected for the general population. Id. (citing Pet. Ex. 58 at 2). Dr. Lancaster found "the study provides better evidence against the idea of vaccines causing myasthenia gravis than for it." Id. He further observed that the study was "very small and subject to reporting bias." Id. Dr. Lancaster opined that the much larger and better peer-reviewed study by Zinman et al. was "far more convincing" and "its conclusions based on sounder methods." Id.

Dr. DeAngelo criticized the studies that did not show any association between the flu vaccine and myasthenia gravis because the studies were too small, to which Dr. Lancaster responded that the medical profession "should rely on the largest and best studies" available. Resp. Ex. D at 2. Although he acknowledged the limitations based on study size, Dr. Lancaster opined that "[i]n a study of a few hundred patients where no risk is detected, the effect would at most be very small." Id.

In summary, Dr. Lancaster stated that the medical literature cited by Petitioner does not provide "convincing evidence that myasthenia gravis is caused or worsened by [the] [flu] vaccination." Resp. Ex. E at 5. "The available studies suggest that seasonal [flu] vaccines do not trigger or worsen myasthenia gravis." Id. at 6.

ii. Loving Factor Five/Althen Prong Two

Dr. Lancaster disagreed that the flu vaccination caused Mr. Smilo's myasthenia gravis because "[t]here is no reliable evidence that the seasonal [flu] vaccine causes myasthenia gravis." Resp. Ex. A at 8. Further, Dr. Lancaster opined that the flu vaccination did not cause Mr. Smilo's myasthenia gravis because onset of the illness occurred before vaccination. Id. at 6-7. Dr. Lancaster also opined that there is no evidence to show that vaccination worsens myasthenia gravis in those patients with the illness. Id. at 8-9; see Resp. Ex. A, Tabs 2, 4; Pet. Ex. 40.

According to Dr. Lancaster, Mr. Smilo's myasthenia gravis began before vaccination and "caused his symptoms of ptosis, double vision, fluctuating weakness, dysarthria[,] and dysphagia. [His] symptoms evolved over several months and varied in severity during this time,

[63] Dr. Lancaster also rejected Dr. DeAngelo's reliance on PANDAS, or Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections, "as an example of molecular mimicry." Resp. Ex. A at 12. The undersigned did not discuss that aspect of Dr. DeAngelo's opinions, as she agrees it is not relevant to the issues here. Therefore, the undersigned will not discuss Dr. Lancaster's responsive discussion.

as commonly occurs with myasthenia gravis." Resp. Ex. E at 6. Dr. Lancaster cited Hehir and Silvestri to explain that myasthenia gravis often presents with "drooping eyelids, [or] double or blurry vision." Id. at 4 (citing Resp. Ex. E, Tab 1 at 1-2). Hehir and Silvestri noted that "[t]he majority of patients with [myasthenia gravis] first present with ocular symptoms," which includes "ptosis and/or diplopia without pupillary abnormalities." Resp. Ex. E, Tab 1 at 1-2.

Additionally, Dr. Lancaster opined that the "[t]he median time to first myasthenic crisis is 8-12 months," and he cited an article by Wendell and Levine for support. Resp. Ex. E at 4 (citing Resp. Ex. E, Tab 2 at 1). Moreover, "myasthenic crisis may be the initial presentation of [myasthenia gravis] in one-fifth of patients." Resp. Ex. E, Tab 2 at 1. Dr. Lancaster opined that "[Mr. Smilo's] symptoms evolved over several months and varied in severity during this time, as commonly occurs with myasthenia gravis." Id. at 6.

Dr. Lancaster disagreed with Dr. DeAngelo that Mr. Smilo's death was in any way caused by the medication azathioprine. Resp. Ex. A at 10-11. Dr. DeAngelo opined that Mr. Smilo's death was attributable to the medication azathioprine, prescribed as treatment for his myasthenia gravis, and that this medication caused or contributed to the development of HCC with obstructive jaundice, which lead to his death. Pet. Ex. 18 at 1, 5; Pet. Ex. 55 at 4. While Dr. Lancaster agreed that "[a]zathioprine can increase the risk of cancer," he explained that "this risk gradually increases with cumulative doses and time" and "the cancer risk of taking the drug for a couple of months is extremely small." Resp. Ex. A at 10.

Further, Dr. Lancaster opined that Mr. Smilo had the liver mass before he began taking azathioprine, as evidenced by a CT scan performed November 17, 2016, which showed liver masses, the largest of which was 5.5 cm. Resp. Ex. A at 10; see Pet. Ex. 5a at 60. A follow-up MRI was recommended, but it was not done. Resp. Ex. A at 10; see Pet. Ex. 5a at 60. Subsequently, Mr. Smilo was diagnosed with HCC, and given this diagnosis, "it is obvious that this was the same tumor" which "had most likely been slowly growing for months prior to November 17, 2016 to reach this size." Resp. Ex. A at 10. Since the tumor was present before the medication was initiated, as evidenced by the CT scan, "it is impossible for azathioprine to have caused the cancer." Id. Mr. Smilo developed obstructive jaundice in March 2017, which Dr. Lancaster opined "is the logical, predictable[,] and normal history of this type of cancer." Id.

Dr. Lancaster disagreed with Dr. DeAngelo's assertions that the tumors seen on Mr. Smilo's initial CT scan on November 7, 2016 were not the same ones seen on the later CT done in March 2017, or that the tumors seen on the second CT were new or different than the earlier tumors. Resp. Ex. C at 2. He also disagreed with Dr. DeAngelo that the liver masses seen on the initial CT scan were benign or underwent malignant transformation due to treatment with the medication azathioprine. Id. Dr. Lancaster found this scenario extremely unlikely given the facts presented here. Id.

According to Greten et al.,[64] cited by Dr. Lancaster, median survival in patients with liver cancer is only 11 months because "liver cancer is aggressive, rapidly progressive[,] and deadly."

[64] TF Greten et al., Survival Rate in Patients with Hepatocellular Carcinoma: A Retrospective Analysis of 389 Patients, 92 Brit. J. Cancer 1862 (2005).

Resp. Ex. A at 10-11 (citing Resp. Ex. A, Tab 6 at 1). Dr. Lancaster believed that "[t]he enlargement of [Mr. Smilo's] tumor [was] very unlikely to have been significantly influenced by [his] myasthenia gravis or its treatment." Id. at 11. Thus, Dr. Lancaster concluded that "[t]here is no plausible connection between the [flu] vaccine and [Mr. Smilo's] death from cancer." Id.

In summary, Dr. Lancaster concluded that more likely than not "[Mr. Smilo] had myasthenia gravis, which caused his symptoms of ptosis, double vision, fluctuating weakness, dysarthria[,] and dysphagia. [His] symptoms evolved over several months and varied in severity during this time, as commonly occurs with myasthenia gravis." Resp. Ex. A at 12-13; Resp. Ex. C at 4; Resp. Ex. D at 3; Resp. Ex. E at 6. Further, Dr. Lancaster did not agree that the vaccination caused or contributed to Mr. Smilo's death. Resp. Ex. A at 13; Resp. Ex. C at 4; Resp. Ex. D at 3-4; Resp. Ex. E at 6. The cause of death was liver cancer, and Dr. Lancaster opined that "[t]here is no reasonable causal connection between [the] [flu] vaccination and [Mr. Smilo's] liver cancer." Resp. Ex. A at 13; Resp. Ex. C at 4; Resp. Ex. D at 3-4; Resp. Ex. E at 6.

iii. Loving Factor Six/Althen Prong Three

Dr. Lancaster opined that the onset of Mr. Smilo's myasthenia gravis was prior to his flu vaccination, and therefore, the vaccination could not have caused his illness. Resp. Ex. A at 6, 13. Dr. Lancaster placed onset of Mr. Smilo's myasthenia gravis when he developed ptosis, explaining that "[p]tosis is a classic symptom of myasthenia" gravis and "often the presenting symptom." Resp. Ex. C at 2.

Dr. Lancaster's opinion that onset predated vaccination on October 17, 2016 was based on the medical records of four different health care providers. Resp. Ex. A at 6-7. The first three are dated November 17, 2016. Id. And the first of these was Dr. Floyd's record stating that Mr. Smilo reported that his right eye droop began three months before. Id. at 6 (citing Pet. Ex. 4 at 27-29). Dr. Floyd also wrote that his dysphagia had been present since endoscopy the previous September. Id. (citing Pet. Ex. 4 at 27-29). The second record is an ED triage note by Nurse Jellison, stating that Mr. Smilo reported "he had been having trouble with [his] right eye for months." Id. at 7 (quoting Pet. Ex. 5a at 40). Mr. Smilo also reported having "some difficulty with speech for the last week, states increasingly constant, [Petitioner] reports worse over the last few days. [Mr. Smilo] states feeling like he had a phlegm ball in the back of his throat, so he had an EGD at the end of September, state[s] . . . worsening problems this week however." Id. (quoting Pet. Ex. 5a at 40). Mr. Smilo reported onset three months prior to this visit on November 17, 2016. Id. (citing Pet. Ex. 5a at 43). Third, while in the ED, Mr. Smilo was seen by Dr. Goebel, who documented that "[three] months ago [Mr. Smilo] noticed [right] drooping eye lid" and "also had trouble swallowing since his endoscopy in September." Id. (quoting Pet. Ex. 5a at 54-55). The fourth note is from Dr. Catalano, the neurologist who diagnosed Mr. Smilo with myasthenia gravis, on December 12, 2016. Id. (citing Pet. Ex. 6 at 12-14). On December 12, 2016, Mr. Smilo reported that he had had trouble swallowing since August 2016, and that he had right eyelid drooping noted by Petitioner in the spring of 2016. Id. (citing Pet. Ex. 6 at 12).

Thus, Dr. Lancaster opined that "these notes [] clearly date ptosis and dysphagia prior to the vaccination." Resp. Ex. A at 7. He placed significant emphasis on Dr. Catalano's records due to his specialty of neurology, and as such, "[h]e was the person best positioned to understand

the diagnosis and ask the most important questions." Id. And Dr. Lancaster did not believe that Dr. Gavin's VAERS report, which was prepared later in time, invalidated the more contemporaneous records. Resp. Ex. C at 2.

As for Dr. Small's argument that Mr. Smilo's did not have ptosis prior to vaccination because his treating optometrist (Dr. Ives) did not document it, Dr. Lancaster disagreed. Resp. Ex. A at 9. Notably, Dr. Lancaster observed that Dr. Ives did not document ptosis even after Mr. Smilo was diagnosed with myasthenia gravis while his other records document ptosis during this time. Id. Further, Dr. Ives did not document a detailed history, or note that he ever questioned Mr. Smilo about ptosis. Id. For these reasons, Dr. Lancaster did not give as much weight to the records of Dr. Ives, and gave more weight to the detailed histories and records discussed above by a nurse and three physicians who all documented a consistent history taken from their patient. Id.

Dr. Lancaster also disagreed with Dr. DeAngelo's position that because Mr. Smilo's ptosis and dysphagia were not documented before vaccination, the post-vaccination records placing onset of these symptoms prior to vaccination are suspect or inaccurate. Resp. Ex. D at 1. For example, on November 17, 2016, Dr. Floyd documented that Mr. Smilo reported that his ptosis had been present for three months. Id. (citing Pet. Ex. 4 at 27). Dr. Lancaster stated that there is no reason to "question Dr. [Floyd's] competence in gathering this history." Id. Moreover, similar histories were recorded by other health care providers. Id. at 2. "The idea that somehow the symptoms need[ed] to be reported prior to vaccination and not just occur prior to vaccination is not [] reasonable . . . ." Id.

Regarding alternative cause for Mr. Smilo's ptosis, Dr. Lancaster explained that ptosis was "the first sign of [Mr. Smilo's] myasthenia [gravis]." Resp. Ex. A at 7. Dr. Lancaster rejected the idea that Mr. Smilo would have developed ptosis "just a few months prior to a myasthenic crisis (with positive AchR antibodies) and then that it coincidentally improved with treatment of [] myasthenia [gravis]." Id.

Lastly, Dr. Lancaster discussed the affidavits of Petitioner and Dr. Gavin. Resp. Ex. E at 2-3. To summarize, in Petitioner's affidavit, dated August 9, 2021, she averred that her husband, Mr. Smilo, had no symptoms of myasthenia gravis before his flu vaccination. Id. at 2 (citing Pet. Ex. 61). Petitioner also had no recollection of telling Mr. Smilo's physicians that he had symptoms before he received the flu vaccination. Id. (citing Pet. Ex. 61). Dr. Gavin's affidavit, dated August 13, 2021, indicated that he did not see Mr. Smilo when he presented to the office on November 17, 2016, and that the note was made by another physician, Dr. Floyd, who is no longer with the practice. Id. (citing Pet. Ex. 62). In the affidavit, Dr. Gavin interpreted Dr. Floyd's note. Id. (citing Pet. Ex. 62). Dr. Gavin also summarized his prior office records and concluded that Dr. Floyd's noted stating that Mr. Smilo had a droopy eyelid for three months was "erroneous." Pet. Ex. 62 at 3.

In response, Dr. Lancaster disagreed with Dr. Gavin's interpretation of Dr. Floyd's note and did not believe that it was erroneous. Resp. Ex. E at 2-3. Instead, Dr. Lancaster viewed it as consistent with notes written by other providers on November 17, 2016. Id. at 3. Dr. Lancaster also opined that Dr. Floyd's record included Mr. Smilo's complaint that "he couldn't swallow,"

and that this symptom was "also most likely a symptom of myasthenia gravis." Id. at 2-3. In summary, Dr. Lancaster believed that the contemporaneous medical records were more accurate and reliable than the affidavits made over four years after the events in question. Id.

VI. LEGAL FRAMEWORK

A. Standard of Adjudication—Factual Issues

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

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

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

B. Standards for Adjudication—Causation

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

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

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

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

To receive compensation through the Program, Petitioner must prove either (1) that Mr. Smilo suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—

corresponding to a vaccine that he received, or (2) that Mr. Smilo suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Because Petitioner does not allege Mr. Smilo suffered a Table Injury, she must prove a vaccine Mr. Smilo received caused Mr. Smilo's injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

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

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

C. Standards for Adjudication—Significant Aggravation

The elements of an off-Table significant aggravation case are set forth in Loving. See Loving, 86 Fed. Cl. at 142-44; see also W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the Loving case provides the correct framework for evaluating off-table significant aggravation claims"). The Loving court combined the Althen test, which defines off-Table causation cases, with a test from Whitecotton. Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd sub nom., Shalala v.

Whitecotton, 514 U.S. 268 (1995) (concerning on-Table significant aggravation cases). The resultant test has six components, which are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4).

VII. ANALYSIS

A. Onset

The literature filed by the parties establishes that generally, initial symptoms of myasthenia gravis include drooping of one or both eyelids (ptosis). Pet. Ex. 12 at 1-2. Most patients present with ocular symptoms, including ptosis. Resp. Ex. E, Tab 1 at 1-2. Although there is no documentation in Mr. Smilo's medical records of ptosis prior to the date of vaccination (October 17, 2016), medical records after vaccination from four different health care providers independently document that Mr. Smilo reported that he had the symptom of ptosis several months prior to vaccination.

Approximately one month after vaccination, on November 17, 2016, Mr. Smilo was seen by Dr. Floyd. Her note documents "eye drooping [one] week," as well as "right eye droop [three] months." Pet. Ex. 4 at 27 (emphasis omitted). The same day, Mr. Smilo was seen in the ED for complaints of slurred speech and right side eye droop. Triage Nurse Jellison wrote that Mr. Smilo "states he has been having problems with his right eye for months." Pet. Ex. 5a at 40. Nurse Jellison also reported that "onset time was [three] months ago." Id. at 43. While in the ED, Mr. Smilo was also seen by Dr. Goebel, who wrote, "[three] months ago noticed [right] drooping eyelid." Id. at 55. Moving forward to December 12, 2016, Mr. Smilo saw neurologist Dr. Catalano, who wrote that Mr. Smilo's wife, Petitioner, "noted right eyelid drooping in the spring of 2016." Pet. Ex. 6 at 12.

To the extent that Petitioner's affidavit or Dr. Gavin's affidavit are inconsistent with and/or contradict the health care providers' histories documented in the contemporaneous medical records and objective physical examinations or diagnostic testing, the undersigned defers to the contemporaneous records as the most reliable source of information. See Cucuras, 993 F.2d at 1528 (noting that "the Supreme Court counsels that oral testimony in conflict with

contemporaneous documentary evidence deserves little weight"); Doe/70 v. Sec'y of Health & Hum. Servs., 95 Fed. Cl. 598, 608 (2010); Stevens v. Sec'y of Health & Hum. Servs., No. 90-221V, 1990 WL 608693, at *3 (Cl. Ct. Spec. Mstr. Dec. 21, 1990) (noting that "clear, cogent, and consistent testimony can overcome such missing or contradictory medical records"); Vergara v. Sec'y of Health & Hum. Servs., No. 08-882V, 2014 WL 2795491, at *4 (Fed. Cl. Spec. Mstr. May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded in later medical histories, affidavits, or trial testimony.").

This finding also extends to lay witness affidavits and testimony. Other special masters faced with similar situations have found contemporaneous medical records more persuasive than the affidavits and testimonies of lay witnesses. See, e.g., Rote v. Sec'y of Health & Hum. Servs., No. 90-036V, 1992 WL 165970, at *5 (Cl. Ct. Spec. Mstr. July 1, 1992) (finding the lay witness testimony insufficient to overcome the weight of the contemporaneous medical records); Bergman v. Sec'y of Health & Hum. Servs., No. 90-1252V, 1992 WL 78671, at *4 (Cl. Ct. Spec. Mstr. Mar. 31, 1992) (same); Daiza v. Sec'y of Health & Hum. Servs., No. 90-1188V, 1992 WL 59709, at *4 (Cl. Ct. Spec. Mstr. Mar. 5, 1992) (same).

While the undersigned has reviewed the affidavits of Petitioner and Dr. Gavin on the issue of onset, these accounts were documented in August 2021, almost five years after the events in question. In comparison, the medical records prepared contemporaneously by a nurse and three physicians documented that Mr. Smilo and/or Petitioner reported that his ptosis began three months prior to November 17, 2016. This places onset of the ptosis approximately August 2016, and based on Dr. Catalano's note, as early as spring 2016. The fact that at least three of the four records place onset at the same time (three months before) is compelling evidence, because they are consistent even though they are written by different providers. In their totality, these records provide persuasive evidence of onset. Thus, the undersigned finds that the initial manifestation of Mr. Smilo's myasthenia gravis was ptosis, which occurred three months prior to his presentation at the ED on November 17, 2016, and perhaps as early as the spring of 2016. Regardless of whether onset was spring 2016 or August 2016, onset of Mr. Smilo's myasthenia gravis predated vaccination.

B. Six Month Severity Requirement

To be entitled to compensation, Petitioner must show Mr. Smilo

> (i) suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine, or (ii) died from the administration of the vaccine, or (iii) suffered such illness, disability, injury, or condition from the vaccine which resulted in inpatient hospitalization and surgical intervention.

§ 11(c)(1)(D).

Here, Petitioner must prove by preponderant evidence that Mr. Smilo either "died from the administration of the vaccine," or "suffered such illness, disability, injury, or

condition from the vaccine which resulted in inpatient hospitalization and surgical intervention." Id. at § 11(c)(1)(D)(ii)-(iii).

Petitioner contends that there are two reasons that she has satisfied the Vaccine Act's statutory severity requirement: (1) Mr. Smilo's myasthenia gravis injury "resulted in his hospitalization at Latrobe Area Hospital for myasthenic crisis and surgical intervention by means of PEG tube placement as a result of his severe myasthenic dysphagia;" and (2) "Mr. Smilo's myasthenia gravis was a significant contributing fact in bringing about [his] death" as "detailed in the expert reports of Dr. Small and Dr. DeAngelo." Pet. Mot. at 23.

1. Inpatient Hospitalization and Surgical Intervention

First, with regard to "inpatient hospitalization," Petitioner contends "Mr. Smilo's alleged vaccine-related myasthenia gravis/myasthenic crisis resulted in him being admitted for inpatient care at Latrobe Hospital from December 22, 2016 through January 13, 2017." Pet. Reply at 1. During this hospitalization, on January 3, 2017, Mr. Smilo underwent PEG tube placement surgery "to improve his declining health and alter the course of his myasthenic dysphagia." Id. at 2. And after, Mr. Smilo remained hospitalized for monitoring of his postoperative condition. Id. Thus, Petitioner concludes this hospitalization meets the definition of "inpatient hospitalization." Id.

Next, Petitioner relied upon Spooner to interpret whether Mr. Smilo's PEG tube placement surgery constitutes a "surgical intervention." Pet. Reply at 2 (citing Spooner v. Sec'y of Health & Hum. Servs., No. 13-159V, 2014 WL 504728 (Fed. Cl. Spec. Mstr. Jan. 16, 2014)). In Spooner, "surgical intervention" was defined as "the treatment of a disease, injury, and deformity with instruments or by the hand of a surgeon to improve health or alter the course of a disease." Id. (quoting Spooner, 2014 WL 504728, at *10) (citing Leming v. Sec'y of Health & Hum. Servs., 154 Fed. Cl. 325, 332-34 (2021)). Given this definition, Petitioner contends the PEG tube placement would be considered a "surgical procedure" and a "surgical intervention." Id.

Petitioner states the PEG procedure was "surgical" because "(1) it was performed by a surgeon;" "(2) an operative report was authored by the surgeon, Dr. Ted Matthews, to document the procedure;" "(3) it involved the incision and insertion of an instrument into the stomach; namely, an introducer needle with catheter was passed through the incision into the stomach;" "(4) it involved use of anesthesia and Mr. Smilo was taken to postanesthesia care unit for monitoring following the procedure;" and "(5) the hospital treated the procedure as 'surgical.'" Pet. Reply at 3. Petitioner also asserts the PEG tube placement was a "surgical intervention" using the Leming definition: "only those surgical procedures that are administered to directly treat a condition once it has been diagnosed." Id. (quoting Leming, 154 Fed. Cl. at 333). Petitioner explained the PEG tube placement was necessary to treat Mr. Smilo's dysphagia, which was due to Mr. Smilo's myasthenia gravis, and thus, Mr. Smilo's PEG tube placement surgery "meet[s] the definition of 'surgical intervention' as a procedure 'undertaken to alter the course of a disease' and/or 'administered to directly treat a condition once it has been diagnosed.'" Id.

Respondent notes Mr. Smilo's death on April 6, 2017 occurred less than six months after his flu vaccination on October 17, 2016. Resp. Response at 13. Respondent contends that Mr. Smilo's hospitalization and "PEG tube placement does not constitute 'inpatient hospitalization and surgical intervention.'" Id. at 14. Respondent cites three reasons that the PEG tube insertion does not fulfill the Act's third provision related to "inpatient hospitalization and surgical intervention." Id. at 14-17. First, Respondent contends Mr. Smilo's PEG tube placement did not require ongoing hospitalization. Id. at 15. Respondent argues that because Mr. Smilo was already hospitalized for a myasthenic crisis, his PEG tube placement was "inpatient." and "the procedure itself did not necessitate inpatient hospitalization." Id. Mr. Smilo remained hospitalized an additional two weeks after the PEG tube placement for ongoing treatment of his myasthenia gravis. Id.

With regard to "surgical intervention," Respondent contends that a PEG tube placement does not constitute "surgery." Resp. Response at 15. Respondent acknowledges that a surgeon was involved, and that a needle was used, and that these factors weigh in favor of defining the procedure as a surgery. Id. at 15-16. However, Respondent contends that because the procedure was done in an endoscopy suite, that topical lidocaine was used, and because Mr. Smilo received conscious sedation instead of general anesthesia, the facts do not weigh in favor of a finding that the procedure constituted "surgery." Id. at 14-16.

Moreover, Respondent argues that insertion of a PEG tube does not meet the Act's definition of "intervention" because the PEG tube was not "the treatment for Mr. Smilo's [myasthenia gravis]." Resp. Response at 16. In support of this position, Respondent cites the legislative history of the Act, which indicates that the provision "inpatient hospitalization and surgical intervention" was made part of the Act to ensure that surgery for intussusception would be covered, and to serve as a "suitable statutory proxy for a serious injury equivalent to more than six months of pain and suffering." Id. (quoting Spooner, 2014 WL 504728, at *11) (citing Leming, 154 Fed. Cl. at 333-34).

2. Death

Petitioner contends "[her] experts, Dr. Small and Dr. DeAngelo, propose that Mr. Smilo's [flu] vaccine caused or significantly aggravated his myasthenia gravis and this vaccine injury sequela acted in conjunction with his underlying liver cancer to bring about his death." Pet Reply at 3. Petitioner explains the "[flu] vaccine was a substantial factor in causing [Mr. Smilo's] death," and cited Mr. Smilo's death certificate, which listed myasthenia gravis as a "significant condition contributing to death," and the opinions of Dr. Small and Dr. DeAngelo for support. Id. at 3-4 (quoting Pet. Ex. 1 at 1).

Dr. Small opined that "within a reasonable degree of medical certainty[,] [Mr. Smilo's] myasthenia gravis and resulting sequela were a significant contributing factor in bringing about his death." Pet. Ex. 10 at 5. According to Dr. Small, Mr. Smilo's "severe dysphagia did not allow him to tolerate nutrition through normal means of oral feeding requiring gastrostomy tube placement, and a resulting weight loss of 70 pounds." Id. While some of his symptoms improved with treatment, Mr. Smilo's "dysphagia induced weight loss and other myasthenia gravis sequela caused a very weakened and debilitated general state," which made him

"vulnerable to a significant co-existent disease." Id. at 5-6. Mr. Smilo was "diagnosed with liver cancer in early April 2017," and "died on April 6, 2017." Id. at 6. His death certificate indicates that myasthenia gravis was "a significant condition contributing to death." Id. Dr. Small concluded that "[t]he sequence of events from [flu] vaccination to development of significant generalized myasthenia gravis resulted in a rapid and pronounced decline in his overall health and must be considered a significant contributing factor in bringing about his death." Id. Dr. Small holds this opinion regardless of whether the vaccination caused or significantly aggravated Mr. Smilo's myasthenia gravis. Id.

Similarly, Dr. DeAngelo opined that Mr. Smilo's reaction to his vaccination was "the original precipitating event that led to [his] eventual decline from [myasthenia gravis] and eventual death from a combination of his debilitated state and advanced HCC." Pet. Ex. 18 at 15. By the time that Mr. Smilo was diagnosed with cancer, he had "severe dysphagia with an inability to eat[] and resultant PEG tube placement," with a resulting weight loss of 70 pounds. Id. "His debilitated state, along with his immunosuppression, further accelerated his decline and precluded aggressive treatment of his [then] advanced malignancy." Id.

In addition to his opinion that Mr. Smilo's myasthenia gravis led to a debilitated state that contributed to his death, Dr. DeAngelo also opined that Mr. Smilo "may have never developed HCC if he had not been treated with [] azathioprine prescribed to treat his aggressive myasthenia symptomatology." Pet. Ex. 18 at 15. He cited Buell et al., who "report[ed] that azathioprine promotes carcinogenesis independent of its immunosuppressive effects." Pet. Ex. 55 at 2 (citing Pet. Ex. 56 at 4) (internal quotation marks omitted). Buell et al. also states that azathioprine, an antimetabolite, "has long been recognized as an etiologic factor in the development of neoplasia." Pet. Ex. 56 at 4. The authors note its role in the "increased risk of late nonmelanotic skin malignancies" as well as the "development of myelodysplastic syndrome." Id. However, the authors did not state that azathioprine causes or contributes to the development of or rapid progression of liver cancer. Overall, Dr. DeAngelo associates Mr. Smilo's rapid progression of his liver cancer to the medication azathioprine. See Pet. Ex. 55 at 2; Pet. Ex. 18 at 15.

Respondent contends "[t]here is no reliable evidence that Mr. Smilo's [myasthenia gravis] was either a but-for cause or a substantial factor in bringing about his death." Resp. Response at 17. First, Respondent cites to the death certification and argues that it did not indicate myasthenia gravis "medically contributed to his death." Id. "There is no autopsy report, medical analysis, or other reasoned explanation supporting the notion that Mr. Smilo's [myasthenia gravis] was contributory." Id. Additionally, Respondent contends it is not clear who filled out the death certificate "or how the cause of death was determined," when in comparison, the medical records "list only liver failure from HCC as his cause of death, and do not mention [myasthenia gravis]." Id.

Respondent next argues Dr. Small's and Dr. DeAngelo's opinions are "vague," "speculative" and "implausible," and "do not describe how Mr. Smilo's [myasthenia gravis] or its sequela led, in any medically or scientifically cognizable way, to the liver cancer that caused his death." Resp. Response at 18 (emphasis omitted). With regard to Dr. DeAngelo's argument that the medication azathioprine advanced Mr. Smilo's cancer, Respondent notes "Dr. Lancaster [] explained[] studies have shown that cancer rates detectably increase only for patients who

have been on azathioprine for five to 10 years," and "Mr. Smilo had a large liver mass on a CT done in November 2016, prior to starting azathioprine, and was only on the medication for approximately two months." Id. And given the size of the mass, Dr. Lancaster opined it had been growing for months prior. Id.

Thus, Respondent concludes Petitioner did not provide evidence that Mr. Smilo's myasthenia gravis or its sequelae were both a but-for cause and a substantial factor in bringing about his death. Resp. Response at 20-21.

3. Analysis

This case presents the novel question of whether a PEG tube insertion for treatment of dysphagia, caused by Mr. Smilo's myasthenia gravis, constitutes "surgical intervention" under the Act. The Vaccine Act does not define the phrase "surgical intervention," and therefore, the words will be given their "ordinary, contemporary, common meaning," unless Congress expressed some intent that the phrase should have a particular meaning. Leming, 154 Fed. Cl. at 331 (quoting Williams v. Taylor, 529 U.S. 420, 431 (2000)) (citing Niz-Chavez v. Garland, 141 S. Ct. 1474 (2021)).

As explained by Chief Judge Kaplan in Leming, this statutory provision was added to the Vaccine Act in 2000 to provide for a new category of petitioners to be entitled to compensation. Leming, 154 Fed. Cl. at 332. The pre-2000 Act allowed compensation for those injuries that caused death or lasted six months or longer. Id. In 2000, this additional provision was added, allowing compensation to petitioners who had a vaccine injury that "resulted in inpatient hospitalization and surgical intervention." Id.

In 2000, the year the Act was amended, the definition of the word "surgery" in Dorland's Illustrated Medical Dictionary ("Dorland's") was the same as it is now: "the branch of medicine that treats diseases, injuries, and deformities by manual or operative methods." Leming, 154 Fed. Cl. at 332; Surgery, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=48252 (last visited May 3, 2023). In 2000, and now, operation includes "any act performed with instruments or by the hands of a surgeon." Leming, 154 Fed. Cl. at 332; Operation, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=35203 (last visited May 3, 2023). In Leming, Chief Judge Kaplan also referenced the definition from the American Medical Association ("AMA"), which defines surgery as that performed by a licensed physician "for the purpose of structurally altering the human body by the incision or destruction of tissues." Leming, 154 Fed. Cl. at 332 (quoting Surgery, Am. Med. Ass'n Pol'y Finder, https://policysearch.amaassn.org/policyfinder/detail/surgery? uri=%2FAMADoc%2FHOD.xml-0-4317.xml (last revised April 2007)). The AMA statement further provides that surgery is "the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transposition of live human tissue which include lasers, . . . scalpels, probes, and needles." Id. (quoting Surgery, Am. Med. Ass'n Pol'y Finder, https://policysearch.amaassn.org/policyfinder/detail/surgery? uri=%2FAMADoc%2FHOD.xml-0-4317.xml (last revised April 2007)).

The facts here establish that Mr. Smilo underwent two PEG tube insertions, during two different hospitalizations. The first operation was January 3, 2017, during Mr. Smilo's initial hospitalization for myasthenia gravis. Mr. Smilo's medical records include an "operative report" for his PEG tube insertion, which establishes that both a surgeon, Dr. Matthews, and a gastroenterologist, Dr. Klions, were present for the procedure. Pet. Ex. 5a at 273. The name of the procedure performed was "[EGD] with placement of a gastrostomy tube." Id. And gastrostomy is a "surgical creation of an artificial opening into the stomach." Gastrostomy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=19901 (last visited May 3, 2023).

In addition to the surgeon and gastroenterologist, there was an anesthesiologist, and the anesthesia type was MAC, and midazolam, lidocaine, and propofol were administered. The operative note states that "[a]fter adequate sedation" was obtained, an endoscope was placed by Dr. Klions (gastroenterologist) and "positioned in the midportion" of the stomach, "directed towards the anterior abdominal wall." Pet. Ex. 5a at 274. "A polypectomy snare was passed into the stomach by [Dr. Klions], [and] opened fully . . . ." Id. On the outside of the abdominal wall, the surgeon, Dr. Matthews, took the following action: "[t]he overlying skin was anesthetized with lidocaine and 0.5 cm incision[65] was made." Id. After the abdominal wall was incised by Dr. Matthews, he introduced a needle with overlying catheter and passed it "through this incision and into the stomach under visualization with the endoscope." Id. The gastrostomy tube was then inserted as described in the operative report. Id. Mr. Smilo was taken to post-anesthesia care unit. Id. The record indicates that there were no intraoperative complications. Id. "Dr. Matthews and Dr. Klions were present . . . for the entirety of the procedure." Id. Anesthesia postoperative note by Dr. Sadler documented that the patient had "[n]o [a]pparent [c]omplications" of anesthesia. Id. at 284.

Mr. Smilo underwent another PEG tube insertion during his last hospitalization. On April 4, 2017, Mr. Smilo underwent PEG replacement because his first PEG tube had become dislodged. The procedure was performed by surgeon Dr. Rabinovitz and gastroenterologist Dr. Das.[66] The procedure was performed under MAC. The operative note verified that the former PEG tube was misplaced, stating that "[t]here was evidence of a gastrostomy with no G-tube present in the gastric body." Pet. Ex. 16a at 91. The surgeon "create[ed] a new tract for G-tube placement" at a different site in the abdominal wall into the stomach. Id. A "trocar needle was introduced into the abdominal wall and into the stomach under direct endoscopic view," and a G-tube was placed. Id. "The old G-tube was removed[,] and a dressing placed at the site." Id. at 92.

Using the definitions described above, both PEG tube insertions qualify as "surgery." They were both performed by surgeons, described as operations, and operative reports were

[65] The operative note does not state what instrument was used to make this incision into the stomach. Presumably, however, a scalpel or similar instrument was used.

[66] Mr. Smilo also underwent an ERCP with placement of two stents at the same time. That procedure is not discussed here.

prepared for both procedures. In both procedures, an incision was made on the outside of the abdominal wall into the stomach, and instruments, including scalpels and/or needles were used to incise the skin and stomach. Thus, the undersigned finds that Mr. Smilo underwent two surgical procedures, as contemplated by the Act.

The second part of the question is whether the two PEG tube surgeries constituted "interventions" under the Act. The current Dorland's definition and the 2000 Dorland's definition of "intervention" is "the act or fact of interfering so as to modify," and "specifically, any measure whose purpose is to improve health or to alter the course of a disease." Intervention, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=25701 (last visited May 3, 2023); Leming, 154 Fed. Cl. at 333.

Regarding the question of whether the procedure constituted an "intervention" for treatment of Mr. Smilo's myasthenia gravis, the following facts are relevant. The literature establishes that the "hallmark" of myasthenia gravis is "muscle weakness that worsens after periods of activity and improves after periods of rest." Pet. Ex. 12 at 1. "Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often . . . involved in the disorder." Id. Dysphagia, or difficulty swallowing, is a symptom of the disease. Id. Mr. Smilo reported a history of difficulty swallowing when he presented to neurologist Dr. Catalano on December 12, 2016. Pet. Ex. 6 at 12. Dr. Catalano's neurological examination revealed "severe dysphagia." Id. at 13. Mr. Smilo's condition worsened, and he was hospitalized on December 22, 2016. Pet. Ex. 5a at 109, 127, 137. During his hospitalization, his dysphagia did not improve, and he had a PEG tube inserted for "progressive dysphagia. He failed swallow evaluation and modified barium swallow and had aspiration and penetration." Id. at 113, 125. His discharge note states, "Dysphagia. The patient had a PEG tube placed. This is all secondary to his myasthenia gravis." Id. at 125.

The records establish that Mr. Smilo's dysphagia was caused by his myasthenia gravis. The PEG tube was inserted to treat his dysphagia (inability to swallow) due to the weakness of the relevant muscles caused by his myasthenia gravis. As such, the two PEG tube surgeries were measures designed to improve Mr. Smilo's health, by allowing him to eat and receive medications for his illness. Fundamentally, the PEG tube was an intervention for his dysphagia, and his dysphagia was directly caused by myasthenia gravis. Therefore, the undersigned finds that the two PEG tube procedures which Mr. Smilo underwent constituted "surgical interventions," pursuant the Vaccine Act. These "surgical interventions" also resulted in inpatient hospitalizations" pursuant to the Vaccine Act. Thus, Petitioner has satisfied the severity requirement of the Act.

Because the undersigned finds Petitioner has satisfied the "resulted in inpatient hospitalization and surgical intervention" requirement, the undersigned does not reach the second issue of whether Mr. Smilo's myasthenia gravis "was a significant contributing fact in bringing about [his] death," so as to satisfy the severity requirement of the Vaccine Act.

C. Significant Aggravation

1. Loving Factor 1: What Was Mr. Smilo's Condition Prior to Administration of the Vaccine?

The first step in the Loving test is to determine Mr. Smilo's condition prior to the vaccination he received on October 17, 2016. Prior to vaccination, Mr. Smilo had a history of hypertension, low back pain, and esophageal reflux. In May 2016, he was seen by Dr. Gavin for treatment of malaise, cough, nasal congestion, and fever, and Dr. Gavin diagnosed an upper respiratory infection. Mr. Smilo saw Dr. Gavin again on August 22, 2016, complaining of dysphagia, hoarseness, and cough. Dr. Gavin ordered an EGD. Approximately one week later, on September 1, Mr. Smilo was seen by Dr. Mejia for low back pain and complained of trouble with swallowing. He returned to see Dr. Mejia on September 26, 2016 for low back pain and reported hoarseness and pain on swallowing.

In addition to the records summarized, post-vaccination records refer to relevant events that occurred prior to vaccination. Approximately one month after vaccination, on November 17, 2016, Mr. Smilo was seen by Dr. Floyd. Her note documents that he reported ptosis of his right eye that began three months before the visit. The same day, Mr. Smilo was seen in the ED for complaints of slurred speech and right side eye droop. Triage Nurse Jellison documented that Mr. Smilo reported problems with his right eye for months. Also, while in the ED, Mr. Smilo was seen by Dr. Goebel, who noted that Mr. Smilo noticed his right eyelid drooping three months before.

The undersigned finds, consistent with her onset ruling, that the onset of Mr. Smilo's myasthenia gravis was before vaccination, and that he had right eyelid drooping, trouble swallowing, hypertension, low back pain, and esophageal reflux prior to vaccination. While he had not yet been diagnosed with myasthenia gravis, he did have symptoms of the illness.

2. Loving Factor 2: What Is Mr. Smilo's Current Condition (or His Condition Following the Vaccination, If Also Pertinent)?

The second part of the Loving test is to discuss "the person's current condition (or condition following the vaccination if that is also pertinent)." Loving, 86 Fed. Cl. at 144. Here, Mr. Smilo's condition following vaccination is most pertinent.

Approximately one month after vaccination, on November 17, 2016, Mr. Smilo was seen by Dr. Floyd, who documented that he had ptosis and slurred speech. Diagnostic workup ultimately revealed a diagnosis of myasthenia gravis. On December 22, 2016, his condition worsened, requiring hospitalization and PEG tube placement. After treatment and discharge, he remained stable until March 2017, when he was diagnosed with liver cancer.

3. Loving Factor 3: Does Mr. Smilo's Current Condition (or Condition After Vaccination) Constitute a "Significant Aggravation" of His Condition Prior to Vaccination?

The next factor of the Loving test is to determine whether there is a "significant aggravation" of Mr. Smilo's condition by comparing his condition before vaccination to his condition after vaccination. The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4). Using this definition, the undersigned finds that, based on the facts and circumstances here, Mr. Smilo had a significant aggravation of his underlying myasthenia gravis which progressed over time as described in the medical records, within the month after vaccination. Thus, Petitioner meets the criteria of Loving Factor Three.

4. Loving Factor Four/Althen Prong One: Medical Theory of Causation

The fourth Loving factor has its origins in Althen Prong One, and Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. See Andreu, 569 F.3d at 1379; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner has failed to establish a sound and reliable medical theory for how the flu vaccination can cause significant aggravation of myasthenia gravis by preponderant evidence for the reasons discussed below.

Both Dr. Small and Dr. DeAngelo embraced molecular mimicry as the most common causal theory used to explain how infections or vaccines cause autoimmune illnesses. And they cite medical literature that discussed molecular mimicry in general terms in the context of infections and vaccines. None of the articles cited, however, establish that molecular mimicry has been posited as a causal mechanism for how the flu vaccine could cause myasthenia gravis. For example, Dr. DeAngelo discussed the Schwimmbeck et al. paper. But Schwimmbeck et al. reported a homologous protein between an AChR epitope and a herpes simplex virus glycoprotein. Dr. DeAngelo did not offer any explanation of how these findings could be extended to the flu vaccine.

Opining that molecular mimicry is a causal theory, without more, is insufficient. See, e.g., McKown v. Sec'y of Health & Hum. Servs., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (explaining that "merely chanting the magic words 'molecular mimicry' in a Vaccine Act case does not render a causation theory scientifically reliable, absent additional evidence specifically tying the mechanism to the injury and/or vaccine in question" (emphasis omitted)); Johnson v. Sec'y of Health & Hum. Servs., No. 14-254V, 2018 WL 2051760, at *26 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) ("Petitioners cannot simply invoke the concept of molecular mimicry and call it a day. Rather, they need to offer reliable and persuasive medical or scientific evidence of some kind (whether expert testimony or literature) . . . ." (internal citations omitted) (emphasis omitted)); Mattus-Long v. Sec'y of Health & Hum. Servs., No. 15-113V, 2022 WL 4242140, at *27 (Fed. Cl. Spec. Mstr. Aug. 31, 2022) (noting "the mere mention of molecular mimicry is not a 'get out of jail free card' in the Program, entitling claimants to compensation, merely because it has scientific reliability as a general matter"); Sheets v. Sec'y of Health & Hum. Servs., No. 16-1173V, 2019 WL 2296212, at *17 (Fed. Cl. Spec. Mstr. Apr. 30, 2019) (determining Petitioner had not satisfied Althen Prong One when he did not relate molecular mimicry "to either the vaccines in question or Petitioner's own specific condition").

When Dr. Lancaster questioned Petitioner's experts' reliance on molecular mimicry, Dr. DeAngelo then suggested the theory of haptenization. There are, however, several problems with this theory. First, haptenization is a novel concept for explaining how a vaccine could cause an autoimmune illness, and specifically, how the flu vaccine could cause myasthenia gravis. Based on the literature cited by Dr. DeAngelo, and Dr. Lancaster's expert reports and opinions about the theory, it does not appear that the process of haptenization has previously been suggested as a mechanism by which a vaccine could cause an autoimmune illness. The literature filed by Dr. DeAngelo about haptens and haptenization does not discuss post-vaccination autoimmune illnesses or myasthenia gravis. Since Dr. DeAngelo's theory based on haptenization in the context of post-vaccination autoimmune illnesses was not published in any of the medical articles filed in this case, no evidence has been filed to show that the theory has previously been identified, or is known or accepted by the medical community. Therefore, it is difficult to conclude that the theory is "sound or reliable." See Boatmon, 941 F.3d at 1359 (explaining the theory need not be medically or scientifically certain, but must be "sound and reliable"); see also Knudsen, 35 F.3d at 548 (same).

In addition, the haptenization theory described by Dr. DeAngelo has been taken out of the context in which it was presented and discussed in the medical literature. Generally, the articles cited by Dr. DeAngelo about haptenization describe research using haptens to create immunogenic proteins or vaccines for treatment of tumors or certain types of cancers. These vaccines are not used to prevent infectious diseases, like the flu vaccine here; instead, they are developed to delay or slow tumor growth. Dr. DeAngelo does not explain how the vaccine, or any component of vaccine, could form a drug-protein conjugate so as to create an autoimmune illness in humans.

Further, Dr. DeAngelo changes the meaning of Bugelski by amending the words in the figures and in the paragraphs describing the figures and adding content and conclusions that were

not mentioned or discussed by Bugelski. This type of mischaracterization adversely affects the persuasiveness of Dr. DeAngelo's opinions.

In summary, Bugelski discusses how non-immunogenic xenobiotics, small molecules that do not cause an immune response, can become linked to a protein, and through a complex process, and with the interaction of metabolic enzymes, can ultimately cause an immune response. Bugelski does not describe how vaccines generally, or the flu vaccine, could, through haptenization, create an immune response that could lead to the development of myasthenia gravis. Thus, the undersigned finds that Bugelski, and the theory of haptenization, is not relevant, and does not explain how a flu vaccine could cause myasthenia gravis.

The same is true of Dr. DeAngelo's concept of the neo-antigen, which he asserts is capable of inducing autoimmunity based on articles by Bolon, Berd, and Berd et al. A neo-antigen is defined in Dorland's as "a new antigenic determinant, such as a tumor-associated antigen, that is formed when a protein is modified by metabolic processes or that emerges when a conformational change exposes a previously unexpressed epitope." Neoantigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=33398 (last visited May 3, 2023). However, Dr. DeAngelo offers no evidence that the flu vaccine is subject to haptenization, as discussed above, or that this process creates a neo-antigen that could play some role via molecular mimicry to cause myasthenia gravis.

According to Dr. DeAngelo, the process of haptenization "contorts the three-dimensional confirmation for self-proteins, exposing previously hidden epitopes and rendering them immunogenic." Pet. Ex. 63 at 2. However, Bolon, Berd, and Berd et al. do not discuss this concept in the context of vaccines that protect against infectious illnesses. Bolon explains that the conjugation of a hapten usually involves a reactive metal or small chemical, not a vaccine, and not the flu vaccine. The discussion of haptens in Berd and Berd et al. relates to the development of anticancer vaccines, called hapten-modified tumor vaccines. The flu vaccine is not a hapten-modified tumor vaccine.

As explained by Dr. Lancaster, the theory of haptenization posits "that [flu] proteins can act as haptens, that this hapten formation would specifically occur with the [AChR], and that this can actually cause myasthenia gravis." Resp. Ex. C at 3. Dr. Lancaster further opines that "[t]his is a complex chain of improbable events offered without any supporting evidence." Id. The undersigned agrees.

Regarding the theory of bystander activation, Dr. DeAngelo defines it in his expert reports as nonspecific activation of previously quiescent immune cell lines, but he does not develop the theory or describe how it would lead to myasthenia gravis. The same is true of his references to superantigens, polyclonal activation, and epitope spreading. He mentions the concepts, but in a conclusory manner, without development or explanation of how they could cause or aggravate myasthenia gravis after a flu vaccination. The medical literature cited by Dr. DeAngelo in support of these additional theories does not support the notion that they play a role in disease development after vaccination. For example, Bernasconi et al. discusses polyclonal activation, but not in the context of vaccination. Lehmann et al. and Smatti et al. discuss the

concept of epitope spreading, but they do not discuss vaccines, or explain how vaccines could cause myasthenia gravis.

The reference to superantigens seems wholly inappropriate. Superantigen is defined as "any of a group of powerful antigens occurring in various bacteria and viruses that binds outside of the normal T-cell receptor site and is able to react with multiple T-cell receptor molecules of a given β-chain variable element, regardless of their α-chain sequence, thus activating T cells nonspecifically. Included are staphylococcal enterotoxins and toxins causing toxic shock syndrome and exfoliative dermatitis." Superantigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=48059 (last visited May 3, 2023). There is no evidence here that the flu vaccine elicited a response like that caused by a superantigen. And there is no evidence that myasthenia gravis is caused by superantigens, or a similar process triggered by superantigens, resulting in an overwhelming systemic illness like toxic shock syndrome.

While it may not be inappropriate to offer several alternative causal theories in support of vaccine causation, Petitioner's approach of identifying a novel theory and then adding a handful of additional theories without development reduces the persuasiveness of the opinions offered. See Baron v. Sec'y of Health & Hum. Servs., No. 14-341V, 2019 WL 2273484, at *17 (Fed. Cl. Spec. Mstr. Mar. 18, 2019) ("Although Petitioners . . . do not need to provide the specific components of the mechanism by which the vaccine[] at issue can cause [the alleged injury], they do need to propose something more than taking a vague 'kitchen sink' approach and listing eleven mechanisms that have been previously submitted in the Program for claims of vaccine-caused injury with various degrees of success. Petitioners have listed many possibilities but have not identified a sound and reliable explanation that can be applied to the vaccines and injury in this case.").

Moreover, the medical articles do not support a finding that the flu vaccination can cause or significantly aggravate myasthenia gravis. While there are some case reports of new onset myasthenia gravis following vaccinations, there appears to be only one case report of significant aggravation, and it was after a hepatitis B vaccination, not a flu vaccination. In 1998, Domigo et al. reported one case of new onset myasthenia gravis and one case of significant worsening in a patient with pre-existing myasthenia gravis following receipt of hepatitis B plasma vaccine. The patient whose condition worsened one month after vaccination had been diagnosed five years prior to her worsening condition. Pet. Ex. 14 at 1. This same case report was briefly noted by Stübgen, in 2010, when he summarized hepatitis B vaccination and myasthenia gravis. Pet. Ex. 39 at 3. Other than this one patient, the medical articles do not report any other cases where a patient with pre-existing myasthenia gravis worsened after receiving a vaccination.[67]

[67] Petitioner did file case reports of new onset myasthenia gravis following vaccinations, and articles about the same subject. Some of the articles did not contain sufficient detail to discern whether the patients experienced new onset versus exacerbation of their illness. For example, the abstract by Sanghani et al. reporting on VAERS data seems to discuss only newly diagnosed patients but it is not entirely clear. See Pet. Ex. 15.

In contrast, there are three studies of patients with pre-existing myasthenia gravis who received the flu vaccine. All three showed that vaccination did not worsen the clinical course of patients with existing myasthenia gravis. The first of these was a population-based study in Canada from Zinman et al. using vaccination records and hospital admission information for 3,667 hospital admissions from 1992 to 2007. Resp. Ex. A, Tab 4 at 1. No association was found "between receipt of [flu] vaccine and hospitalization for [myasthenia gravis] among patients with the disease." Id. at 4. The second study, from Tackenberg et al. in 2018, was a double-blind, randomized, placebo-controlled study done in Germany over three consecutive years in 62 patients, half of whom received the flu vaccine. Pet. Ex. 40 at 1. Vaccination did not cause a clinically relevant increase in antibody titer or exacerbate the clinical course of the patients with myasthenia gravis. Id. at 6-7. A similar study was undertaken in the Netherlands by Strijbos et al. in 2019. Resp. Ex. A, Tab 2. In that study, they examined 47 patients, who received a placebo or a flu vaccine, and obtained the same result—that is, "[flu] vaccination [did] not induce an immunological or clinical exacerbation of [] [myasthenia gravis]." Id. at 1.

While these studies involved small numbers of patients and had other limitations, they are the best evidence available on the question of whether the flu vaccine can exacerbate myasthenia gravis. Given the paucity of case reports showing that flu vaccination has been shown to worsen existing myasthenia gravis, they support the undersigned's finding that the Petitioner has failed to prove by preponderant evidence that the flu vaccine can significantly aggravate myasthenia gravis.

Lastly, there is a dearth of similar cases. In one reasoned decision involving myasthenia gravis, Burch, the Petitioner sought compensation on behalf of her minor child after she developed myasthenia gravis following a varicella vaccination. Burch ex rel. K.A.F. v. Sec'y of Health & Hum. Servs., No. 99-520V, 2007 WL 1673512, at *1-2, *18 (Fed. Cl. Spec. Mstr. May 23, 2007). The facts and circumstances here are very different than in Burch, and therefore, it is difficult to apply the reasoning in it to this case. Briefly, the records in Burch established that in March 1996, prior to vaccination, the child had varicella lesions (chickenpox) after exposure to her brother while he had chickenpox. Id. at *1. As a result of her prior infection, Petitioner's expert testified that the child was "primed" for a quicker response after subsequent exposure to the virus. Id. at *8. Approximately five months later, the child received a varicella vaccine (August 15, 1996) and within several days, she had symptoms that were subsequently diagnosed as consistent with myasthenia gravis. Id. at *2. Petitioner's expert opined that there were three precipitating causes for the child's myasthenia gravis: (1) her prior episode of varicella (when she had chickenpox), (2) a respiratory infection two weeks before vaccination, and (3) her varicella vaccination. Id. at *7-9. The special master agreed and awarded compensation to Petitioner. Id. at *16-18.

In Burch, however, the child did not have onset of symptoms prior to vaccination, there was no claim of significant aggravation, a different vaccine was at issue, and there were three contributing causes of myasthenia gravis. Here, there is no expert opinion suggesting that there were three precipitating factors at play (one of which was vaccination) that combined to bring about Mr. Smilo's myasthenia gravis. Moreover, Ms. Smilo's onset of myasthenia gravis preceded vaccination and he received a different vaccine. Thus, the undersigned does not find the reasoning applied or the ruling relevant here. Moreover, the undersigned is not bound by

decisions of other special masters. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

In Kelly, the petitioner alleged his myasthenia gravis was caused-in-fact by flu vaccination. Kelly v. Sec'y of Health & Hum. Servs., No. 16-1548V, 2023 WL 3274159, at *1 (Fed. Cl. Spec. Mstr. May 5, 2023). The special master in Kelly found Petitioner was unable to prove by preponderant evidence that his myasthenia gravis was caused-in-fact by his flu vaccine, and as such, dismissed his case. Id. at *12. Specifically, the special master determined petitioner "fail[ed] to link the [flu] vaccine to myasthenia gravis in any meaningful way," specifically noting the role of molecular mimicry in such a case is "unsettled," and as such the expert's opinion was not found "sound and reliable." Id. at *9-10. Although the undersigned is not bound by decisions of other special masters, the undersigned finds this finding informative as similar medical literature filed in Kelly was relied upon in this case. See Boatmon, 941 F.3d at 1358; Hanlon, 40 Fed. Cl. at 630. Additionally, unlike Petitioner here, the petitioner in Kelly did not have myasthenia gravis prior to vaccination. Kelly, 2023 WL 3274159, at *10. And although the petitioner in Kelly developed myasthenia gravis within a medically acceptable timeframe, a temporal relationship alone is insufficient. Id. at *11-12.

Overall, the undersigned finds that here, Petitioner's theories are unsupported by medical or scientific facts, research, or any other reliable evidence. Moreover, the theories are speculative and/or conclusory in nature. When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck v. Sec'y of Health & Hum. Servs., No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, decision aff'd, 141 Fed. Cl. 138 (2018), aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert." Prokopeas v. Sec'y of Health & Hum. Servs., No. 04-1717V, 2019 WL 2509626, at *19 (Fed. Cl. Spec. Mstr. May 24, 2019) (quoting Moberly, 592 F.3d at 1315). Instead, special masters are expected to carefully scrutinize the reliability of each expert report submitted. See id.

Therefore, the undersigned finds that Petitioner has not established by preponderant evidence that the flu vaccine can cause or significantly aggravate myasthenia gravis.

5. Loving Factor Five/Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, and Loving Factor Five, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

Regarding the fifth Loving factor/second Althen prong, the undersigned finds that because Petitioner failed to prove by preponderant evidence that the flu vaccination can cause or

significantly aggravate myasthenia gravis, she is also unable to prove that the vaccination caused or significantly aggravated Mr. Smilo's myasthenia gravis. There are additional reasons why Petitioner has failed to prove this element of her claim.

First, because the undersigned finds that onset of Mr. Smilo's myasthenia gravis occurred before vaccination, his flu vaccination could not have caused his illness. Therefore, the question is whether there is a logical sequence of cause and effect to show that Mr. Smilo's vaccination caused a significant aggravation of his myasthenia gravis.

Dr. Lancaster provides the most cogent, sound, and reliable opinions on this aspect of causation, and the undersigned therefore finds his opinions most persuasive. He explained that the symptoms of myasthenia gravis evolve over time and vary in severity, like they evolved in Mr. Smilo's case. The medical literature supports this opinion. Patients who present with ocular symptoms, like Mr. Smilo, often develop more generalized disease. Myasthenia crisis is also likely to occur early in the diseases process, and usually in the first three years. Accordingly, Dr. Lancaster's opined that Mr. Smilo's illness evolved as would be expected, and not because of his flu vaccination. The undersigned finds this reasoning to be sound.

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

Mr. Smilo saw many different physicians over the course of his illness, including the neurologist who diagnosed his myasthenia gravis, and none of them documented an opinion stating that his flu vaccine caused or worsened his myasthenia gravis.

Dr. Floyd saw Mr. Smilo one month after vaccination on November 17, 2016, and although she questioned whether he could have myasthenia gravis, she assessed him with stroke-like symptoms and referred him to the ED for a work-up. She did not reference the flu vaccine. In the ED, Mr. Smilo saw Dr. Goebel, who like Dr. Floyd, took a history dating symptoms back three months. Dr. Goebel did not mention the flu vaccine. Next, Dr. Smilo saw Dr. Gavin on December 7, 2016. Dr. Gavin noted that Mr. Smilo had a "bulbar voice," but he did not question

or attribute causation to the flu vaccine.[68] Pet. Ex. 4 at 24. Mr. Smilo's treating neurologist, Dr. Catalano, did not attribute causation to the flu vaccine.

During subsequent hospital admissions, Mr. Smilo was seen by many physicians, including specialists, and there are no references to suggest that any of them thought that the flu vaccine played any causal role in the cause or worsening of his myasthenia gravis.

On April 3, 2017, Mr. Smilo saw oncologist Dr. Rajagopal for treatment of his liver cancer. Dr. Rajagopal stated, "[p]atient reports developing [myasthenia gravis] in the setting of a flu shot in October; however, we do not have full information about diagnosis. Myasthenia gravis has also been reported in [one] case report in the literature as being associated with HCC." Pet. Ex. 16a at 38. This note suggests that Dr. Rajagopal questioned whether Mr. Smilo's myasthenia gravis was associated with his HCC, not his flu vaccination.

The undersigned finds this statement regarding the development of myasthenia gravis in the setting of a flu shot, without more, does not meet the level of preponderant evidence. See § 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.67 (2009) ("[T]here is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted."); Robertson v. Sec'y of Health & Hum. Servs., No. 18-554V, 2022 WL 17484980, at *17 (Fed. Cl. Spec. Mstr. Dec. 7, 2022) (explaining "the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases"); Hibbard v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 742, 749 (2011) (finding it neither arbitrary nor capricious for a special master to weigh competing treating physicians' conclusions against each other), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Caves v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 119, 136 (2011), aff'd, 463 F. App'x 932 (Fed. Cir. 2012).

For these reasons, the undersigned finds that Petitioner has failed to provide preponderant evidence of Loving Factor Five/Althen Prong Two, that Mr. Smilo's myasthenia gravis was caused or significantly aggravated by his flu vaccination. Since the undersigned finds that Petitioner did not prove by preponderant evidence that the flu vaccine caused or worsened Mr. Smilo's myasthenia gravis, she need not reach the question of whether any medication prescribed for his myasthenia gravis caused or worsened his liver cancer.

6. Loving Factor Six/Althen Prong Three: Proximate Temporal Relationship

The last element in the six-part Loving test has origins in Althen Prong Three. As stated in Loving, this element is "a showing of a proximate temporal relationship between vaccination and the significant aggravation." Loving, 86 Fed. Cl. at 144. Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the

[68] Although Dr. Gavin filed a VAERS report, he does not state an opinion about causation in the report. See Pet. Ex. 9. Dr. Gavin also executed an affidavit, but it addresses the question of onset, and does not include an opinion as to causation. See Pet. Ex. 62.

injury alleged. Althen, 418 F.3d at 1281. A proximate temporal relationship has been equated to mean a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

Based on the case law cited above, this factor/prong consists of two parts. Petitioner must first establish the time frame within which it is medically acceptable to infer causation. And secondly, she must show that the onset or worsening/aggravation of Mr. Smilo's illness occurred during this time frame.

Dr. Small opined that Mr. Smilo developed symptoms of myasthenia gravis approximately three weeks after his flu vaccination, which was an appropriate interval for an immune-mediated illness. He did not offer an opinion about what temporal association would be appropriate if Mr. Smilo was found to have onset prior to vaccination or assuming that Petitioner was pursuing a claim based on significant aggravation. Dr. DeAngelo opined that the onset or significant aggravation of Mr. Smilo's myasthenia gravis was approximately three weeks after vaccination, and that this time frame is consistent with the Domigo et al. case report. In the relevant case report, the patient with pre-existing myasthenia gravis worsened in the month after receipt of her second hepatitis B vaccination.

Dr. Lancaster opined that the onset of Mr. Smilo's myasthenia gravis was prior to vaccination, and therefore, vaccination could not have caused his illness. And the undersigned agrees that onset occurred prior to vaccination. Therefore, the relevant question is whether Petitioner has proven that Mr. Smilo's significant aggravation occurred within a relevant time post-vaccination.

The undersigned finds that there is a temporal association between Mr. Smilo's receipt of his flu vaccination and the worsening of his symptoms of myasthenia gravis. However, a temporal association, without more, is insufficient. Moberly, 592 F.3d at 1323; Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[A] proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury."). Thus, Petitioner is not entitled to compensation.

VIII. CONCLUSION

The undersigned extends her sympathy to the Petitioner for the loss of her husband, for the suffering that Mr. Smilo experienced, and for the suffering that Petitioner witnessed while she cared for her husband during his illness. The undersigned's Decision, however, cannot be decided based upon sympathy, but rather on the evidence and law.

For all of the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that the flu vaccination caused or significantly aggravated

Mr. Smilo's myasthenia gravis. Therefore, Petitioner is not entitled to compensation and her petition must be dismissed.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master