In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Originally Filed: December 19, 2019

Refiled in Redacted Form: January 23, 2020

R.S.,	*	PUBLISHED
Petitioner,	*	No. 15-1207V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement Decision; Influenza ("flu") Vaccine; Guillain-Barré Syndrome ("GBS"), Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes ("POEMS") Syndrome; Onset.
Respondent.	*	

Ronald C. Homer, Conway, Homer, P.C., Boston, MA, for petitioner.
Linda S. Renzi, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

I. INTRODUCTION

On October 15, 2015, R.S. ("petitioner") filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"),[2] 42 U.S.C. § 300aa- 10 et seq. (2012), alleging that as a result of receiving an influenza ("flu") vaccine on October 1, 2013, she suffered from Guillain-Barré syndrome ("GBS") and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes ("POEMS") syndrome. Petition at

[1] When this decision was originally filed the undersigned advised her intent to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioner filed a timely motion to redact certain information. This decision is being reissued with initials, R.S. or S., in place of petitioner's name. Except for those changes and this footnote, no other substantive changes have been made. This decision will be posted on the court's website with no further opportunity to move for redaction.

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

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1-2. Respondent argued against compensation, stating that "this case is not appropriate for compensation under the terms of the Vaccine Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 17).

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 the flu vaccine she received on October 1, 2013, caused her injuries. Therefore, entitlement must be denied.

II. PROCEDURAL HISTORY

The petition was filed in this matter on October 15, 2015. Shortly thereafter, on October 26, 2015, petitioner filed seven medical record exhibits. Petitioner's Exhibits ("Pet. Exs.") 1-7 (ECF No. 7). Petitioner filed additional medical records, her supporting affidavit, and a Statement of Completion on October 27, 2015. Pet. Exs. 8-23 (ECF Nos. 9-10); Pet. Aff. dated Oct. 27, 2015 (ECF No. 11). On February 22, 2016, respondent filed his Rule 4(c) Report, recommending against compensation. Resp. Rept. at 2.

A status conference was held in April 2016 to determine next steps in the case, and the parties agreed that petitioner should file an expert report. Order dated Apr. 27, 2016 (ECF No. 18). Petitioner filed two additional sets of medical records on March 26, 2016 and June 6, 2016, respectively. Pet. Exs. 24-28 (ECF Nos. 21, 25). On August 5, 2016, petitioner filed an expert report by Dr. Norman Latov. Pet. Ex. 29 (ECF No. 26). Respondent thereafter filed a responsive expert report by Dr. Dennis Bourdette on January 6, 2017. Resp. Ex. A (ECF No. 33). On January 26, 2017, the undersigned ordered petitioner to file a supplemental expert report addressing the opinions of Dr. Bourdette. Order dated Jan. 26, 2017 (ECF No. 34). Petitioner submitted a supplemental report from Dr. Latov on March 23, 2017. Pet. Ex. 31 (ECF No. 35).

On May 2, 2017, the undersigned held a Rule 5 status conference with the parties. Order dated May 2, 2017 (ECF No. 39). Given the complexities of the case, the undersigned did not offer her preliminary findings. Rather, both parties agreed that expert reports addressing the hematologic aspect of petitioner's claim would be helpful. Respondent filed an expert report by Dr. Brea Lipe on June 16, 2017. Resp. Ex. C (ECF No. 40). On December 4, 2017, petitioner submitted a responsive report from Dr. Latov. Pet. Ex. 38 (ECF No. 54). After a number of months, petitioner filed an expert report from Dr. Samir Parekh on October 11, 2018. Pet. Ex. 57 (ECF No. 75).

On June 20, 2018, the undersigned set this matter for hearing to take place on January 29-30, 2019. Order dated June 20, 2018 (ECF No. 72). The parties completed their respective pre-hearing filings by early January 2019, and the hearing took place as scheduled. The parties filed post-hearing briefs on April 26, 2019 and July 24, 2019, respectively.

This matter is now ripe for adjudication.

III. MEDICAL TERMINOLOGY

As the literature filed in this case establishes, GBS is a peripheral neuropathy involving rapidly-progressive and ascending motor paralysis caused by demyelination of the peripheral nerves. See Pet. Ex. 29, Tab C at S21-S22.[3] The primary clinical features of the disease are generalized muscle weakness combined with sensory symptoms. Id. at S21. Symptoms indicative of GBS typically begin abruptly with paresthesia in the feet, progressing to paralysis of the lower limbs, and ascending to the trunk, limbs, and face. Id. at S21-S22. Weakness of the facial muscles and respiratory complaints are also common features. Id. Patients suffering from GBS typically experience a monophasic course and reach nadir between two and four weeks following onset. Id. at S21. Chronic inflammatory demyelinating polyneuropathy ("CIDP") is a chronic form of GBS, which progresses slowly over time, but manifests similar symptoms. Resp. Ex. E, Tab 1 at 477.[4] Patients with symptoms consistent with GBS, but lasting longer than two months, are typically considered to be suffering from CIDP.

POEMS syndrome, by contrast, is a paraneoplastic syndrome due to an underlying plasma cell disorder. Pet. Ex. 29, Tab F at 214.[5] Typical features of the syndrome include: demyelinating polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Id. The diagnostic criteria for the condition requires a patient to satisfy two mandatory criteria: polyneuropathy and monoclonal gammopathy, along with one of the following: elevated serum vascular endothelial growth factor ("VEGF") levels, sclerotic bone lesions, or Castleman's disease. Id. Additionally, patients suffering from POEMS may have various minor criteria, such as papilledema and thrombocytosis. Id. The progression of symptoms is gradual, with the median time from onset to diagnosis being thirteen to eighteen months. Resp. Ex. C, Tab 4 at 304.[6] Misdiagnosis of the illness is common due to its rarity and multi-system manifestations. Id. The most common misdiagnoses, based on the initial symptoms, include CIDP, diabetes, and nephritis. Id.

Despite their differences, distinguishing between POEMS and GBS/CIDP is difficult during the early phases given the similarities in the initial presenting neuropathy. The literature filed in this matter suggests that over half of POEMS patients presenting with a related polyneuropathy are diagnosed initially with CIDP. Resp. Ex. E, Tab 1 at 477. Clinically, POEMS patients typically experience distal muscle weakness in the lower extremities only, while patients

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[3] Arthur Asbury & David Cornblath, Assessment of Current Diagnostic Criteria for Guillain-Barré Syndrome, 27 Ann. Neurol. S21 (1990).

[4] Saiko Nasu et al., Different Neurological and Psychological Profiles in POEMS Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy, 83 J. Neurol. Neurosurg. Psychiatry 476 (2012).

[5] Angela Dispenzieri, CME Information: POEMS Syndrome: 2014 Update on Diagnosis, Risk-Stratification, and Management, 89 Am. J. Hematol. 213 (2014).

[6] Jian Li & Dao-Bin Zhou, New Advances in the Diagnosis and Treatment of POEMS Syndrome, 161 Brit. J. Hematol. 303 (2013).

with GBS/CIDP experience weakness in both the upper and lower limbs. Id. In addition, patients with POEMS usually complain of neuropathic pain in the lower extremities, whereas patients with symptoms akin to GBS/CIDP rarely complain of pain. Id. Patients whose symptoms are initially believed to be compatible with GBS/CIDP may later be diagnosed with POEMS syndrome based on the subsequent course of illness as additional symptoms manifest.

Although intravenous immunoglobulin ("IVIG") treatments are utilized successfully in resolving both GBS and CIDP, single agent IVIG therapy is not considered to be the most effective treatment for POEMS syndrome. Pet. Ex. 29, Tab F at 220. Case reports, however, do indicate that IVIG treatment can result in a reduction of serum VEGF levels and clinical improvement in some patients. Id. Indeed, even after initial treatment with IVIG therapy, POEMS syndrome will become progressively worse until the proper treatment is administered. Radiation, melphalan-dexamethasone, and corticosteroids typically result in the most noted improvement in the majority of POEMS syndrome cases. Id. at 219-20.

IV. FACTUAL SUMMARY

A. Medical History Prior to Vaccination

R.S. was born on August 23, 1972. Pet. Ex. 3 at 35. Prior to her receipt of the vaccine at issue in this matter, R.S. had no history of neurological abnormalities. Her prior medical history is significant for cherry angiomas, basal cell neoplasms, and depression. Pet. Ex. 2 at 1; Pet. Ex. 3 at 35-36.

B. Receipt of Vaccination and Subsequent Clinical Course

i. Medical Treatment in 2013

R.S. received the flu vaccine at issue herein on October 1, 2013. Pet. Ex. 1 at 1. No adverse reaction was noted at the time of vaccine administration. Id.

On November 6, 2013, roughly four weeks following her vaccination, R.S. presented to Dr. Gopalan Umashanker, a neurologist employed with Cottage Hospital in Woodsville, New Hampshire. Pet. Ex. 6 at 1-2. R.S. complained of weakness and numbness in her legs. Id. at 1. She reported to Dr. Umashanker that three days following her receipt of the flu vaccine, she experienced severe diarrhea and stomach pain that lasted a couple of days. Id. Around October 10, 2013, R.S. reported that she developed numbness in the tips of her toes, which eventually ascended to the pads of her feet and toes. Id.

At the time of her visit with Dr. Umashanker, petitioner's symptoms had progressed over the past week to include pain in the calves and hips, fatigue, palpitations, numbness in the fingers, unsteady gait, and drooling. Pet. Ex. 6 at 1. Upon exam, petitioner's dorsiflexors were noted to be weak, and reflexes in her ankles, biceps, and knees were diminished. Id. at 2. A mid-shin sensory deficit was also noted. Id. Dr. Umashanker assessed R.S. with "probabl[e]" GBS due to the markedly diminished reflexes, sensory deficits, and facial involvement, though it was noted that additional testing would be needed to confirm the diagnosis. Id. R.S. was

admitted to Dartmouth Hitchcock Medical Center ("Dartmouth") that same day for further testing. Id.

Upon admission to Dartmouth, R.S. was seen by a second neurologist, Dr. Elijah Stommel. Pet. Ex. 7 at 1-6. Consistent with the history provided to Dr. Umashanker, R.S. reported that she developed a "GI bug" three days following her receipt of the flu vaccine on October 1, 2013. Id. at 1. By mid-October of that year, she developed toe and finger numbness, calf pain, weakness in the lower extremities, low back pain, palpitations, drooling, and eye strain. Id. at 1-2. Dr. Stommel reviewed R.S.'s history and opined that her course was "concerning for acute inflammatory demyelinating polyneuropathy" or AIDP. Id. at 6. Dr. Stommel further noted the viral illness reported prior to the onset of symptoms which would be consistent with such a diagnosis. Id. A lumbar puncture conducted during R.S.'s hospital stay showed a slightly elevated protein of 57 (range: 15-45) with normal glucose. Id. at 44. An EMG was consistent with a generalized peripheral neuropathy with demyelinating features. Id. at 56. R.S.'s lab tests also indicated that she had thrombocytosis, with an elevated platelet count of 473 x10(3) /mcL. Id. at 4. Her IgA level was within normal limits at 174 (range: 70- 400mg/dL). Id. at 5. R.S. was discharged on November 11, 2013, with diagnoses of GBS and AIDP. Id. at 54. Discharge notes indicated that she received a dose of Solu-medrol (200mg) and a five-day course of IVIG treatment with noted improvement in extremity strength. Id. at 54- 58.

R.S. was hospitalized a second time at Littleton Regional Healthcare ("Littleton Regional") in Littleton, New Hampshire, from November 26-29, 2013, due to difficulties with her speech and gait. Pet. Ex. 5 at 658-59. Upon admission, R.S. reported that she did well over a two-week period, but started to experience increased tingling in the legs and fingers, difficulty walking, chest pain, and voice issues, roughly thirty-six hours prior to presentation. Id. at 658. It was noted that she received a flu vaccine in early October. Id. at 658, 659. Emergency room treaters assessed her with a GBS flare and recommended further treatment with IVIG. Id. at 659. Her thrombocytosis persisted, with labs indicating her platelets remained elevated at 707 K/uL. Id. at 628. On November 27, 2013, Dr. Stephen Goldberg conducted a serum protein electrophoresis ("SPEP") test without immunofixation ("IFE") to test for monoclonal gammopathy. Pet. Ex. 7 at 600. R.S. tested negative for the monoclonal protein, but two beta region peaks were recorded. Id. The assessment remained GBS with treatment related fluctuation. Pet. Ex. 5 at 681. Discharge records indicated that R.S.'s paresthesia and gait improved following IVIG treatment. Id. Her deep tendon reflexes remained absent and she continued to experience residual tingling in the toes. Id.

R.S.'s health continued to worsen. Less than two weeks later, she was readmitted to Littleton Regional on December 10, 2013 for persistent lower extremity weakness, sensory loss, and paralysis in the lower extremities. Pet. Ex. 5 at 544; Pet. Ex. 7 at 324-26. Upon admission, petitioner complained of worsening paresthesia, continued gait abnormalities, and leg pain. Pet. Ex. 5 at 485-87. R.S. received two additional infusions of IVIG at Littleton Regional, with no improvement in strength. Pet. Ex. 7 at 314-16. She was transferred back to Dartmouth on December 12, 2013 for further evaluation and treatment. Id. She finished her five-day course of IVIG at Dartmouth with a steady improvement in strength noted following her

last treatment. Id. at 342. R.S. was discharged on December 15, 2013, with instructions to follow up with her primary neurologist as needed. Id. at 325.

On December 20, 2013, Petitioner presented for a follow-up appointment with Dr. Stommel. Petitioner reported that she continued to experience weakness, but could ambulate well with a walker. Pet. Ex. 7 at 471-72. On exam, Dr. Stommel noted residual complaints, including sensory loss in the lower extremities, weakness in both legs, and subtle weakness in the biceps. Id. at 471. A repeat nerve conduction study revealed a slight worsening in active denervation in the left tibialis. Id. Given the progression of her symptoms, Dr. Stommel recommended that she continue IVIG treatments. Id. Dr. Stommel also prescribed Cellcept. Id. Lab testing conducted on December 26, 2013, and January 15, 2014, indicated that Ms. Saver's thrombocytosis remained persistent with elevated platelet levels of 554 k/uL and 583 k/uL, respectively. Id. at 477, 484. R.S. remained relatively stable throughout the remainder of 2013, though she continued to complain of tremors, foot pain, blurred vision, fatigue, weakness, and diminished sensation in the lower extremities. Pet. Ex. 7 at 478-79.

ii. Medical Treatment in 2014

R.S. presented to Littleton Regional for a fourth hospitalization on January 27, 2014. Pet. Ex. 5 at 63-65, 379. The history recorded at discharge indicated that she was diagnosed with GBS initially on November 6, 2013, and suffered three relapses all of which required IVIG treatment. Id. at 63. Upon admission, R.S. complained of cognitive issues, fever, and chills. Id. at 63-64. She also had "trouble remembering things." Id. at 64. The attending physician diagnosed R.S. with aseptic meningitis secondary to an IVIG infusion she received on January 23, 2014. Id. at 69. An MRI of the thoracic spine showed a spinal cord neoplasm at the T12-L1 level. Id. at 379. The attending neurologist opined that the neoplasm was likely incidental and not related to petitioner's paresthesia, which he deemed to be related to a CIDP diagnosis. Pet. Ex. 5 at 64.

On February 4, 2014, petitioner presented to the Massachusetts General Hospital ("MGH") neuromuscular clinic for an evaluation of her persistent symptoms. Pet. Ex. 8 at 26-30. The health history recorded during this visit indicated that R.S.'s symptoms began with progressive lower limb weakness in October 2013 and thereafter progressed to include severe fatigue, calf pain, gait abnormalities, and sensory deficits. Id. at 26-29. The attending physician, Dr. Michael Bowley conducted a repeat EMG and nerve conduction analysis, both of which continued to show evidence of sensory and motor polyneuropathy. Id. at 8-10. Dr. Bowley concluded that R.S. likely had CIDP, with multiple subsequent relapses, given her clinical history of rapidly evolving motor deficits, distal areflexia, and elevated CSF. Id. at 28. R.S.'s "initial improvement" with IVIG was also considered to be supportive of such a diagnosis; however, Dr. Bowley indicated that her repeated relapses did not respond as well to further IVIG treatment. Id. Dr. Bowley recommended that she increase her mycophenolate dose and use corticosteroids as needed. Id. at 29. Her platelet count remained elevated at 627 k/uL. Pet. Ex. 9 at 131. A SPEP test conducted on February 4, 2014, showed an abnormal pattern of two IgA lambda components at 0.22 and 0.06 g/dL in the beta region, but was negative for monoclonal protein. Pet. Ex. 8 at 3-4.

Petitioner was hospitalized for a thoracic laminectomy and mass resection on February 12, 2014, both of which were unrelated to her underlying disease course. Pet. Ex. 9 at 25, 127-28. Prior to the surgery, her treaters discovered a spinal mass and recommended removal out of concern for lymphoma. Id. at 116-19. Pathologic testing indicated that the mass was a T12 hemangioma. On February 18, 2014, R.S. was transferred to a rehabilitation facility for occupational and physical therapy. Pet. Ex. 10 at 36-39. Upon discharge on March 14, 2014, petitioner could ambulate and transfer with a walker. Id. at 38. Her discharge diagnoses included extradural spinal mass and post-T12 laminectomy, with a secondary diagnosis of GBS/CIDP. Id. at 32.

On May 27, 2014, R.S. presented for a follow-up appointment at MGH with Dr. Jennifer Dineen. Pet. Ex. 8 at 14-18. She reported that she continued to experience fatigue, weakness in her legs, tremors, nerve pain, gait abnormalities, and blurry vision. Id. at 15-16. Her exam revealed a sensory and motor neuropathy with features indicative of a demyelinating polyneuropathy. Id. at 15. Dr. Dineen recommended that R.S. continue Cellcept and maintain Gabapentin as needed. Id. at 18. She also decreased petitioner's Prednisone dosage to 30mg daily. Id. at 18. Dr. Dineen did not think that further IVIG treatment would be helpful at this time. Id.

iii. POEMS Diagnosis and Treatment in July and August 2014

R.S. presented to Littleton Regional Hospital on July 14, 2014, with complaints of postural headaches, diplopia, incontinence, and cognitive issues. Pet. Ex. 22 at 194. Upon admission, petitioner was evaluated by Dr. Umashanker in the emergency room. Id. A lumbar puncture revealed an elevated opening pressure with no white blood cells detected, and a normal total protein at 38 mg/dl. Id. at 195. A brain MRI conducted during the visit was also normal. Id. Given the above, R.S.'s treaters felt her symptoms were consistent with benign intracranial hypertension. Id. Prior to her discharge, R.S. was also evaluated by an ophthalmologist, Dr. Krista Haight, for complaints associated with eye pressure, pain, and hazy vision. Pet. Ex. 53 at 1. Dr. Haight assessed petitioner with papilledema. Id. at 3.

On July 31-August 5, 2014, R.S. presented to MGH for complaints related to persistent headaches and vision changes. Pet. Ex. 18 at 1232. Upon admission, R.S. was evaluated by a neurologist, Dr. Mingming Ning. Id. Cerebrospinal fluid testing was unrevealing. Id. Intake notes indicated that R.S. had symptoms of CIDP-like neuropathy, thrombocytosis, and papilledema. Id. Dr. Ning suspected that R.S. might have POEMS syndrome and he recommended a hematology consult. A SPEP draw with immunofixation, conducted on August 1, 2014, revealed a persistent IgA lambda monoclonal protein with components at 0.15 and 0.06 g/dl. Id. at 1163, 1165. The free light chain evaluation showed normal kappa level, and elevated lambda at 31, which was considered to be within a normal ratio limit. Id. at 1163. It was also noted that R.S. had possible sclerotic lesions in the mandible and right pelvis following a skeletal survey, though a bone scan showed no definitive sclerotic lesions. Id.

R.S. returned to MGH on August 12, 2014. Pet. Ex. 18 at 441, 1152. Upon admission, she complained of lethargy, reduced appetite, and blurry vision. She also reported

that her symptoms of weakness remained stable, though she had lost movement in her right toe. Id. at 441, 1167. Treaters questioned the need to continue Cellcept and Prednisone in light of the alternative treatment plan for suspected POEMS syndrome. Id. at 1086. Petitioner was evaluated by the attending hematologist, Dr. Annemarie Fogerty, on August 13, 2014. Id. at 1163. Dr. Fogerty assessed petitioner with a progressive neuropathy, dual M-spike, and thrombocytosis, concerning for POEMS syndrome. Id. It was noted that petitioner satisfied the two major criteria for the condition (i.e., neuropathy and monoclonal gammopathy), as well as two minor criteria: papilledema and thrombocytosis. Id. Petitioner's VEGF[7] levels, taken on August 14, 2014, were noted to be elevated at 1799 (reference range: 31-86), and the diagnosis of POEMS syndrome was confirmed. Id. at 444, 446.

Prior to her discharge on August 18, 2014, petitioner was evaluated by another hematologist, Dr. Andrew Yee. Pet. Ex. 18 at 1082. Dr. Yee discussed POEMS syndrome with R.S. and explained her course in light of the accepted diagnostic criteria. In his opinion, multiple clinical factors identified in R.S.'s prior history, including: polyneuropathy, IgA lambda gammopathy, markedly elevated VEGF levels, thrombocytosis, and papilledema, supported a POEMS diagnosis. Id. Dr. Yee also discussed treatment options with R.S., including a stem cell transplant. Id. Petitioner's records reveal that Dr. Yee recommended Revlimid and dexamethasone for her POEMS-related symptoms. Id.

iv. Medical Care in 2015 and Current Condition

R.S. underwent an autologous stem cell transplant on January 29, 2015. Pet. Ex. 18 at 385-93. Of note, her VEGF levels improved with treatment. Id. at 386. R.S.'s platelets also returned to normal. Pet. Ex. 19 at 1, 28.

On June 17, 2015, R.S. presented to Dr. Angela Dispenzieri, a hematologist at the Mayo Clinic, for a second opinion regarding her POEMS diagnosis. Dr. Dispenzieri noted that petitioner had been diagnosed with POEMS in August 2014 based on a set of factors, including: demyelinating peripheral neuropathy, IgA lambda monoclonal protein, hypertrichosis, white nails, papilledema, peripheral edema, and thrombocytosis. Pet. Ex. 19 at 27. Dr. Dispenzieri placed the onset of petitioner's illness in October 2013, when she experienced new onset fatigue and numbness/tingling in the feet, along with eruptions of cherry angiomas on the skin. Id. By October/November 2013, her symptoms progressed to include muscle pain, difficulty walking, ascending hip pain, numbness in the fingers, and slight drooling. Id. Her initial hospitalization in November 2013 for presumed GBS/CIDP was noted, along with her initial marked improvement with IVIG treatment.

Following her initial hospitalization, Dr. Dispenzieri noted that R.S.'s course worsened. Pet. Ex. 19 at 27. Additional treatment with IVIG, Cellcept, and Prednisone through 2014 did not result in similar levels of improvement. Id. Following her POEMS diagnosis,

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[7] VEGF levels are elevated in patients diagnosed with POEMS syndrome. See Pet. Ex. 29, Tab F at 215. VEGF is known to target endothelial cells and induce a rapid and reversible increase in vascular permeability. Id. It is expressed by osteoblasts in bone tissue, macrophages, tumor cells, including plasma cells, and megakaryocyte/platelets. Id.

R.S. started treatment with Revlimid and dexamethasone between September 2014 and December 2014, which resulted in a significant decrease in the serum VEGF, but only marginal improvement in her lower extremity neuropathy symptoms. Id. at 28. Further treatment with cyclophosphamide mobilization, high-dose melphalan, and stem cell infusion resulted in good improvement. Id. All in all, Dr. Dispenzieri opined that R.S.'s course was consistent with POEMS syndrome. Id. at 30.

As of May 2015, R.S. continues to be treated for POEMS. Pet. Ex. 18 at 562. She routinely experiences fatigue, intermittent headaches, hot flashes, foot swelling and discomfort, and diminished strength in both feet. Id. at 563-64. A neurological exam conducted on May 29, 2015 showed normal function apart from marked weakness and sensory loss in the lower limbs. Id. at 565. Her gait was also improved. Id.

V. Fact and Expert Testimony

A. Fact Witnesses

i. Russell S., M.D.

Dr. S., petitioner's husband, testified about her health history and course following her receipt of the flu vaccine at issue herein. Tr. 139. Prior to receiving the flu vaccine, Mr. S described petitioner as healthy and physically active. Tr. 142. She enjoyed skiing, hiking, completing household tasks, and spending time with the family dogs. Tr. 142, 144. R.S. worked as a medical assistant/consultant with a primary focus on electronic medical record training and administration. Tr. 143. Dr. S. testified that petitioner's position as a consultant was demanding, but she enjoyed the social interaction and travel-related responsibilities. Tr. 143-44.

Dr. S. next recalled petitioner's deterioration in health following her receipt of the flu vaccine. Tr. 145. He testified that petitioner returned from a work conference shortly after receiving the flu vaccine, at which time she began complaining of calf pain and numbness in the feet. Id. Given his medical training, Dr. S. suspected that petitioner might have GBS, but she initially attributed these early-in-time symptoms to travel fatigue or perhaps the wearing of high-healed shoes. Tr. 145-46.

According to Dr. S., petitioner first sought treatment for her symptoms around the beginning of November 2013. Tr. 146. He recalled that petitioner complained of persistent calf, upper leg, and back pain. Id. She had also fallen several times at work. Tr. 146-47. Her symptoms rapidly progressed to include numbness and tingling in the feet, ankles, and hands. Tr. 147. Petitioner also experienced paralysis, drooling, palpitations, nerve pain, and breathing difficulties, which prompted her initial emergency room visit on November 6, 2013 to Dartmouth Hitchcock. Tr. 147-48.

During her initial hospitalization, Dr. S. recalled that petitioner's symptoms improved immediately upon receiving IVIG treatment. Tr. 150. She gained back much of her strength following two to three doses. Id. Upon discharge, R.S. needed assistance with

standing. Tr. 151. She also experienced problems with her balance. Id. Otherwise, she returned home following clearance by her physical and occupational therapists. Id.

In the days following her initial hospitalization, Dr. S. stated that petitioner expressed concern regarding the length of time of her recovery. Tr. 152. Petitioner's recovery remained steady and she expressed interest in returning to work. Id. Roughly two weeks later, however, she experienced a relapse in symptoms. Id. The pain, numbness, and weakness started in her feet and progressed up her body. Id. Petitioner was hospitalization a second time, but improved following additional rounds of IVIG treatment. Tr. 153. Dr. S. recalled that both he and petitioner understood her recovery would be gradual, but they both expected a full recovery consistent with a GBS course. Tr. 53-54.

Following a third hospitalization, Dr. S. recalled that petitioner's treaters expressed some skepticism regarding the progression of her symptoms, as such treatment-related fluctuations attributable to GBS did not usually progress for extended periods of time. Tr. 154. Dr. S. recalled that petitioner's doses of IVIG administered during the third hospitalization did not result in the same improvement as the previous infusions. Tr. 155-56. According to Dr. S., around December 2013, petitioner's diagnosis changed to CIDP, which he understood to be a chronic form of GBS. Tr. 160. He recalled that petitioner's treaters recommended a change in medication to include steroids and Cellcept. Id.

Consistent with the medical records detailed above, Dr. S. recalled that petitioner was assessed for other health concerns as her course progressed (primarily during January 2014). Tr. 160. Specifically, petitioner developed aseptic meningitis following a rapid administration of IVIG. Tr. 160-61. Treaters also identified thoracic lesions following a full-body MRI, which resulted in a lymphoma work-up and lesion removal thereafter in February of that year. Tr. 161-62. Petitioner's surgery and weakened state resulted in an extended stay in a rehabilitation facility throughout March, April, and May 2014. Tr. 163.

Dr. S. next recalled petitioner's course throughout July and August 2014, along with her initial diagnosis of POEMS. Tr. 163. Dr. S. recalled that petitioner began to complain of a significant increase in angiomas, weight loss, fatigue, and further gait abnormalities throughout this time period. Tr. 163-65. In July 2014, petitioner also began to experience intercranial pressure, which resulted in a brain shunt, and papilledema. Tr. 165-66. Following a hematologic consult in August of that year, Dr. S. recalled that petitioner's treaters suspected she had POEMS due to her elevated platelet levels and serum VEGF. Tr. 166.

Dr. S. also attended petitioner's appointment at the Mayo Clinic with Dr. Dispenzieri. Tr. 167. According to Dr. S., petitioner's treaters recommended she see Dr. Dispenzieri given her extensive experience with POEMS patients and the overall rarity of the disease. Tr. 168. In his view, petitioner scheduled the visit to discuss the best treatment protocol moving forward. Id. He did not recall Dr. Dispenzieri discussing the onset of petitioner's POEMS or her initial GBS diagnosis. Tr. 168-69.

Given the extent of her health deterioration over the course of 2013 and 2014, Dr. S. testified that petitioner continues to experience a number of ongoing physical disabilities due to

her condition. Tr. 172. She has fatigue, pain, and balance issues. Tr. 172, 176. These ailments require routine maintenance, including daily medication. Tr. 176-77. Due to the pressure on her brain, petitioner underwent a surgical procedure to insert a brain shunt which helped with her balance. Tr. 176. She also continues to suffer from anxiety and depression. Tr. 172-73. Dr. S. expressed concern regarding petitioner's health in the long term given her persistent physical limitations and mental health issues. Tr. 177-78.

ii. R.S.

Petitioner, R.S., also testified at hearing. Tr. 179. Her testimony largely consisted of her own recollections of her overall health history prior to receiving the flu vaccine, as well as descriptions of the symptoms that followed. Prior to October 2013, petitioner described herself as healthy, physically active, and outgoing. Tr. 181, 184. She worked as a medical assistant/consultant and enjoyed the travel and social interaction her job required. Tr. 181-82, 184-85.

Petitioner recalled the day she received the vaccine at issue in this matter. Tr. 186. She described the day as normal. Id. She did not experience any unusual symptoms during vaccine administration or in the days immediately thereafter. Id. Petitioner stated that she first began to experience adverse symptoms, such as numbness in the feet and fatigue, roughly two weeks post vaccination. Tr. 186-88.

By early November 2013, however, R.S. recalled that her symptoms progressed to include gait and swallowing abnormalities, pain, numbness in the fingers and legs, and drooling. Tr. 188-89. Following initial treatment with IVIG, petitioner testified that she felt "remarkably better." Tr. 191. Petitioner reported that she could ambulate with a walker and regained some of her upper body strength upon discharge. Tr. 192. Despite her symptoms, petitioner's treaters indicated to her that she should expect to recover fully, though the overall healing would take time. Id. Following two additional hospitalizations for a relapse of symptoms, R.S. recalled that IVIG treatment seemed to be less effective. Tr. 193-95.

Leading up to her POEMS diagnosis in August 2014, Petitioner testified that she began to experience head pain/cranial pressure and papilledema in the summer of 2014. Tr. 195-96. She recalled the day her treaters recommended a blood draw to measure her serum VEGF. Tr. 198. Roughly two weeks later, she was diagnosed with POEMS syndrome. Id.

R.S. next recalled her visit with Dr. Dispenzieri at the Mayo Clinic. Tr. 199. She stated that her treaters recommend she see Dr. Dispenzieri given her expertise in the disease. Id. Petitioner reported that that she discussed various treatment options with Dr. Dispenzieri to determine how best to proceed with the overall management of the disease. Id. Despite her satisfaction with Dr. Dispenzieri's recommendations, R.S. took issue with some of the visit notes indicating that her POEMS syndrome began in late 2013. Tr. 200. Rather, R.S. reported that she may have felt "run down" from working, but she did not recall experiencing any other adverse symptoms apart from normal angiomas. Tr. 201.

Consistent with Dr. S.'s testimony, petitioner reported that she continues to suffer from adverse symptoms related to her illness. Tr. 201-02. She attends multiple doctor visits to manage her symptoms. Tr. 204. For instance, Petitioner noted that she has undergone a shunt placement procedure and stem cell transplant to help abate her disease progression. Tr. 203. She also continues to suffer from depression. Id. All in all, R.S. expressed frustration in her inability to work, to take part in outdoor activities, and to actively participate in family life. Tr. 203-04.

B. Expert Witnesses

i. Norman Latov, M.D.

Dr. Latov provided an opinion on petitioner's behalf as to the etiology of R.S.'s condition, along with the flu vaccine's purported role in causing her symptoms. Dr. Latov opined that R.S. was properly diagnosed with GBS, which was vaccine-caused, and that her subsequent diagnosis of POEMS was caused by GBS. Tr. 33-34, 52. Dr. Latov filed three expert reports in support of his medical theory of causation. See Pet. Exs. 29, 31, 38.

Dr. Latov obtained his medical degree from the University of Pennsylvania. Tr. 7; Pet. Ex. 30 at 1. After medical school, Dr. Latov went on to complete a neurology residency and immunology fellowship at Columbia University. Tr. 7. He then joined the faculty at Columbia, where his research and teaching responsibilities focused on autoimmune neuropathies. Tr. 7-8. At present, Dr. Latov serves as a Professor of Neurology and Neuroscience, and the Director of the Peripheral Neuropathy Center, at Cornell University. Tr. 8. His clinical duties include supervising medical students and attending to patients in the neuropathy center. Tr. 8-9. Dr. Latov estimated that his clinic practice represents sixty percent of his current work. Tr. 9. He testified that he treats patients with all forms of neuropathy, including GBS and CIDP. Tr. 11. He also follows roughly ten patients with POEMS syndrome. Id. Dr. Latov also conducts research in the fields of neurology and neuroimmunology, and he is board certified in neurology and psychiatry. Tr. 8-9.

To begin, Dr. Latov reviewed R.S.'s symptoms and the progression of her condition compared to the most common features of GBS. Dr. Latov defined GBS as an acute, or rapidly progressive neuropathy, in which the immune system attacks the myelin component of the peripheral nerves. Tr. 13, 21; Pet. Ex. 29 at 7. A typical GBS course includes generalized weakness, tingling, pain, unsteady gait, cranial nerve involvement, and loss of bowel function. Tr. 14. Demyelination of the nerve can also result in secondary axonal loss, which leads to chronic muscle atrophy and weakness. Tr. 21. GBS is distinguished from other types of neuropathies by using an array of diagnostic testing, including a physical exam, nerve conduction studies, CSF analysis, and MRI imaging. Tr. 13. The condition is routinely treated with plasmapheresis or IVIG. Tr. 15.

Dr. Latov next discussed petitioner's health history in the weeks prior to her first hospital admission on November 6, 2013, and its relationship to her initial GBS diagnosis and subsequent progression of symptoms. Based on his review of the medical record, Dr. Latov recalled that petitioner developed neuropathy-related symptoms, including progressive weakness and

paresthesia in the hands, two weeks following her receipt of the flu vaccine on October 1, 2013. Tr. 12-13. She also complained of calf pain, ascending hip pain, numbness in the fingers, and drooling, all of which Dr. Latov characterized as typical GBS-related symptoms. Tr. 13-14.

Dr. Latov relied heavily on petitioner's contemporaneous diagnostic testing in formulating his opinion regarding her October and November 2013 neuropathy symptoms. As the medical record reveals, the testing completed during petitioner's initial hospitalization showed an increased CSF protein, but no inflammatory changes. Tr. 12. EMG and nerve conduction studies were also consistent with a GBS diagnosis. Id. Petitioner thereafter experienced a rapid improvement in strength following treatment with IVIG therapy. Tr. 13, 15; see Pet. Ex. 7 at 3-4, 14.[8] Given the above, Dr. Latov posited that petitioner's early symptoms were consistent with GBS and he felt that her treating physicians correctly identified the diagnosis and treated her appropriately. Tr. 15.

Following her initial diagnosis, Dr. Latov reported that petitioner experienced two presumed GBS-related relapses. Tr. 12; Pet. Ex. 29 at 9-10. After her second hospital admission, Dr. Latov noted that petitioner received additional rounds of IVIG therapy with noted improvement in her muscle strength. Tr. 17-18; see Pet. Ex. 5 at 662-64; Pet. Ex. 17 at 18. Similarly, in his view, petitioner responded well to IVIG treatment following her third relapse. Tr. 18-20; see Pet. Ex. 17 at 8, 18; Pet. Ex. 7 at 322. Due to her protracted course, Dr. Latov categorized these relapses as "GBS with treatment-related fluctuation." Tr. 20 ("each treatment seems to result in improvement for about two weeks, and then she would relapse'), 21.

As her course continued to deteriorate, Dr. Latov noted that petitioner's diagnosis changed to CIDP around mid-December 2013 due to the repeated relapses outlined above. Tr. 22; Pet. Ex. 29 at 10. Dr. Latov described CIDP as a "sort of chronic" GBS. Tr. 22. In his experience, patients suffering from GBS relapses extending beyond two months are best categorized as experiencing CIDP. Id. Indeed, the medical literature cited by Dr. Latov defines CIDP as immune-mediated neuropathy with an initial phase lasting more than two months, whereafter the course may be relapsing-remitting, steadily progressive, or monophasic. See Pet. Ex. 29, Tab O at 1680.[9] Consistent with R.S.'s treaters, Dr. Latov posited that he would have designated a change in her diagnosis to CIDP at this time given her persistent symptoms. Tr. 22.

By July 2014, R.S. was diagnosed with POEMS syndrome. Tr. 22, 50. Dr. Latov described POEMS syndrome as a plasma cell disorder of unknown etiology. Tr. 58-59. Traditionally, the disorder is accompanied by a slowly progressive, demyelinating neuropathy associated with a lambda monoclonal gammopathy and increased serum levels of VEGF. Tr. 23-24, 55; Pet. Ex. 29 at 7. The diagnostic criteria for the disease require a combination of

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[8] In addition to IVIG, Dr. Latov noted that petitioner received a dose of Solu-medrol, a steroid treatment not typically used to treat GBS. Tr. 16. He suspected that R.S. received this treatment for her neuropathy-related pain. Id.

[9] L. Ruts et al., Distinguishing Acute-Onset CIDP From Fluctuating Guillain-Barré Syndrome: A Prospective Study, 74 Neurol. 1680 (2010).

neuropathy, monoclonal gammopathy, and elevated VEGF, or the presence of Castleman's disease. Tr. 23, 58; see Pet. Ex. 29, Tab F at 214. Other systemic manifestations can include fluid overload, ascites or papilledema, intercranial pressure, skin changes, and endocrine abnormalities. Tr. 23. Dr. Latov posited that patients with POEMS are typically treated with Revlimid or lenalidomide. Tr. 25.

Consistent with petitioner's treating physicians, Dr. Latov agreed that R.S. met the diagnostic criteria for a POEMS syndrome diagnosis by July or August 2014. Tr. 24, 50. In reference to the medical record, Dr. Latov recalled that petitioner presented with a small IgA, lambda monoclonal gammopathy in February 2014. Tr. 24. She thereafter developed papilledema, and was found to have elevated serum VEGF levels in August 2014. Tr. 24, 50.

Based on his interpretation of the medical records, Dr. Latov posited that R.S. developed two separate disease processes over the course of her illness: GBS and POEMS syndrome. Tr. 23; Pet. Ex. 38 at 2. At the same time, Dr. Latov explained that petitioner's GBS evolved into CIDP and then POEMS, resulting in some overlap in the conditions. Tr. 23 ("she probably had POEMS syndrome and CIDP concurrently") 33, 61. Given the accompanying neuropathy that is typically associated with GBS/CIDP and POEMS syndrome, Dr. Latov opined that the diseases are difficult to distinguish clinically at onset.

Despite the similarities, Dr. Latov adamantly maintained that R.S.'s initial symptoms in October and November 2013 were not evidence of an onset of POEMS. Tr. 35, 52, 54-55, 69; Pet. Ex. 29 at 9. In so stating, Dr. Latov dismissed opinions from petitioner's later-in- time treating physicians who placed her onset of POEMS syndrome in October 2013 close-in- time to her initial neuropathy and eruption of cherry angiomas. Tr. 46-47, 49. Rather, he maintained that the first manifestation of POEMS syndrome occurred in July/August 2014 when R.S. experienced increased cranial pressure/papilledema, and her bloodwork indicated an increase in serum VEGF levels and the presence of monoclonal gammopathy. Tr. 55-56, 85.

Dr. Latov next discussed the medical record evidence he deemed supportive of his opinion that R.S.'s initial neuropathy-related symptoms, beginning in October 2013, were indicative of GBS as opposed to POEMS syndrome. Dr. Latov opined that a neuropathy associated with POEMS syndrome is typically chronic or subacute in nature and nonresponsive to treatment with IVIG therapy. Tr. 24-25, 35. In contrast, a neuropathy associated with GBS is acute, or rapidly progressive, and responds well to IVIG. Tr. 57-58.

In R.S.'s case, Dr. Latov concluded that her initial neuropathy was best attributable to GBS given the rapid progression of symptoms and her positive response to IVIG therapy. In support, Dr. Latov referenced instances in the medical records where petitioner's treaters reported an improvement in muscle strength over the course of her hospital admissions. He maintained on cross examination that R.S.'s response to IVIG as a whole, or over the course of her three hospitalizations, was consistent over the active course of her GBS and the related relapses, despite some suggestion by respondent that the treatment gradually became less robust. Tr. 36.

On cross examination, Dr. Latov was questioned further regarding the effectiveness of IVIG and plasmapheresis in patients with POEMS syndrome. Tr. 36. For instance, respondent offered a study authored by Dr. Latov, and submitted into evidence by petitioner, which reports that patients with monoclonal gammopathy can experience some clinical improvement following IVIG and plasmapheresis therapy. Tr. 36-37; see Pet. Ex. 29, Tab H.[10] Dr. Latov acknowledged the study, but maintained that neuropathies associated with POEMS syndrome do not respond well to IVIG treatment. Tr. 37-38, 39. He explained that treatment effectiveness depends on the type of monoclonal gammopathy experienced and the underlying disease process associated with its occurrence. Id. For example, monoclonal gammopathies related to GBS or CIDP will respond well to IVIG, whereas classic POEMS does not. Tr. 36-37, 38-39. In support, Dr. Latov cited to case reports of POEMS patients reporting an improvement in GBS-related symptoms following treatment with IVIG. See, e.g., Pet. Ex. 29, Tab Q;[11] Resp. Ex. A, Tab 10;[12] Resp. Ex. A, Tab 6.[13]

In addition to her initial neuropathy, Dr. Latov recalled that petitioner experienced cranial nerve symptoms, such as drooling, during her first hospital admission. Tr. 24, 76, 85. Based on his review of the literature, Dr. Latov opined that cranial nerve involvement is not typically associated with POEMS syndrome. Tr. 24-25. He estimated that older POEMS literature identifies cranial nerve involvement as a presenting symptom in one percent of cases. Tr. 59-60. He further reported that updated literature discussing POEMS syndrome does not implicate the cranial nerve. Tr. 59, 76-77; see Resp. Ex. A, Tab 6 at 678. GBS, on the other hand, is more often associated with the cranial nerve. Tr. 14, 24, 55, 76. Dr. Latov thus concluded that petitioner cranial nerve symptoms were likely attributable to GBS. Tr. 55, 76.

Dr. Latov downplayed the significance of R.S.'s cherry angioma eruption, occurring simultaneous with her neuropathy. Tr. 47, 61. At hearing, he estimated that fifty percent of the population experiences cherry angiomas, a condition which is routinely unrelated to some underlying disease process. Tr. 47, 61; see Pet. Ex. 31, Tab R at 905. Dr. Latov further posited that POEMS syndrome is associated with "glomerulus angioma[,]" which petitioner did not have. Tr. 47, 63-64; see Pet. Ex. 31, Tab N at 1349.[14] Given the prevalence of angiomas,

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[10] Norman Latov, Pathogenesis and Therapy of Neuropathies Associated with Monoclonal Gammopathies, 37 Ann. Neurol. S32 (1995).

[11] Monika Sojka et al., Guillain-Barré Syndrome as the First Manifestation of POEMS Syndrome, 46 Neurologia i Neurochirurgia Polska 284 (2012).

[12] Ju-Hong Min et al., POEMS Syndrome Presenting with Acute Demyelinating Polyneuropathy: Increased Terminal Latency Indices and Uniform Demyelination, 52 Intern. Med. 1513 (2013).

[13] S. Isose et al., POEMS Syndrome with Guillain-Barré Syndrome-Like Acute Onset: A Case Report and Review of Neurological Progression in 30 Cases, 82 J. Neurol. Neurosurg. Psychiatry 678 (2010).

[14] Rachel Miest et al., Cutaneous Manifestations in Patients with POEMS Syndrome, 52 Int'l J. Dermatol. 1349 (2013).

Dr. Latov could not conclude that this symptom more likely than not supported a finding of an onset of POEMS in October/November 2013. Tr. 47-48.

To further distinguish between R.S.'s initial GBS diagnosis and her development of POEMS syndrome, Dr. Latov spent some time at hearing discussing the relevance of petitioner's SPEP test results. Tr. 43-44. R.S.'s initial SPEP test, conducted in November 2013, was negative for the monoclonal protein, a finding that suggested petitioner did not have POEMS around that time period. Tr. 43 ("serum protein electrophoresis was negative without an M protein"); see Pet. Ex. 7 at 600. On cross examination, however, Dr. Latov agreed that a small number of POEMS patients can present with normal SPEP. Tr. 43-44, 85-86. He further acknowledged that the SPEP test petitioner received in early November 2013 was conducted without immunofixation, the preferred method to test for monoclonal gammopathy. Tr. 43.

On cross examination, respondent questioned Dr. Latov regarding the significance of R.S.'s persistent thrombocytosis and its relationship to her POEMS syndrome diagnosis. Tr. 44. Dr. Latov agreed that thrombocytosis can be a presenting symptom in both GBS and POEMS. Id. He estimated that fifty percent of patients with an inflammatory condition experience thrombocytosis. Id. Once the inflammation is treated, the platelet count returns to normal in most cases. Id. Dr. Latov acknowledged that R.S. presented with an elevated platelet count during her first hospitalization for neuropathy symptoms in November 2013, which progressed through 2014. Tr. 45. He could not recall if petitioner's count improved following her treatment for POEMS syndrome. Id.

Dr. Latov next proposed a medical theory of causation by which the flu vaccine caused R.S. to develop GBS, and thereafter, POEMS syndrome: the biologic process of molecular mimicry accompanied by chronic immune stimulation. Tr. 26. Dr. Latov's testimony on molecular mimicry theory revolved around a concept that has largely been accepted in the medical community, and often in the Vaccine Program, as a causal mechanism for a flu vaccine-induced GBS injury. In short, Dr. Latov proposed that antibodies produced to fight off a foreign antigen/infection or generated in response to a vaccine can mistakenly attack, or cross-react with the myelin basic protein, a primary component of the human nerves. Tr. 26-27. As a result, an autoimmune process begins, which further promotes the production of these antibodies that then mistakenly attack the self, thereby causing damages to the nerve's myelin sheath.[15] Tr. 27; see Pet. Ex. 29, Tab P at 105.[16]

Dr. Latov acknowledged at the hearing that he is not proposing that the flu vaccine caused petitioner's POEMS syndrome. Tr. 55, 72-73. But rather, as noted earlier, he theorized that petitioner's POEMS syndrome was a direct result of GBS, which he deems vaccine-induced,

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[15] At hearing, Dr. Latov briefly referenced the concept of bystander activation as a possible mechanism by which the flu vaccine could initiate an autoimmune reaction via autoreactive immune cells (produced secondarily to those responding to the foreign antigen). Tr. 26; see Pet. Ex. 29 at 8.

[16] Lawrence Schonberger et al., Guillain-Barré Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1977, 110 Am. J. Epidemiol. 105 (1979).

a theory he acknowledged has *not* been described in the medical literature to date as an established mechanism for pathogenesis. Tr. 33, 54, 56-57. To causally connect plasma cell disorders or plasma cell "dyscrasia" to GBS, Dr. Latov posited that an over-production of plasma cells is thought to be secondary to the chronic stimulation of B-cells which resulted from petitioner's GBS. Tr. 33, 50-51. When asked to describe how GBS could trigger POEMS, Dr. Latov stated that "if the monoclonal gammopathy happens to be lambda light chain and associated with [] the VEGF and the other cytokines, it can by chance, become POEMS." Tr. 31. Dr. Latov posited that while chronic stimulation is necessary to initiate POEMS, the monoclonal gammopathy can self-perpetuate once its "in place" without further immune stimulation. Tr. 67.

Dr. Latov's testimony regarding the role of cytokines in his theory was vague. He explained that proinflammatory cytokines are produced by the immune system in response to a foreign antigen invasion. Tr. 32. Dr. Latov could not recall if cytokines are pathologically associated with the onset of GBS, but he theorized that the IL-6 cytokine may induce abnormal levels of VEGF which is related to POEMS syndrome. Tr. 32, 59. Despite these assertions, Dr. Latov did not cite to any studies supporting a theory that cytokines can result in elevated serum levels of VEGF. Tr. 32. He also acknowledged that anti-cytokine agents do not ameliorate the clinical manifestations of POEMS syndrome. Id.

At hearing, Dr. Latov discussed multiple medical articles that he stated supported his theory that a plasma cell disorder, such as POEMS syndrome, could result from the chronic inflammation produced secondary to GBS. Tr. 28. First, Dr. Latov referenced the Di Troia article. Id.; see Pet. Ex. 29, Tab E.[17] The Di Troia article correlated the clinical and electrophysical features of neuropathy with the duration and anti-neural activity of the M-protein in seventeen patients to determine the pathogenic relevance of an IgG monoclonal gammopathy. Pet. Ex. 29, Tab E at 64. Dr. Latov posited that the Di Troia study is relevant to the present matter because it shows that a monoclonal gammopathy can occur simultaneous with a neuropathy. Tr. 28, 81. Indeed, the authors of Di Troia reported that all patients included in the study were diagnosed with a neuropathy prior to onset of a monoclonal gammopathy. Pet. Ex. 29, Tab E at 66. They concluded, however, that the "pathogenic relevance of this association is . . . unknown." Id. at 70. Dr. Latov acknowledged this conclusion at hearing, and agreed that further investigation is needed to determine how the two disease processes are related. Tr. 66.

Dr. Latov next discussed the McShane article. Tr. 29-30; see Pet. Ex. 31, Tab M.[18] The McShane article catalogs the current literature undertaken to evaluate the strength of evidence linking autoimmune disease with an elevated risk of monoclonal gammopathy and multiple myeloma. Pet. Ex. 31, Tab M at 332. Dr. Latov posited that researchers in McShane found an elevated risk of both monoclonal gammopathy and multiple myeloma in the presence of autoimmune disease. Tr. 29. Notably, however, researchers in McShane could not identify a

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[17] A. Di Troia et al., Clinical Features and Anti-Neural Reactivity in Neuropathy Associated with IgG Monoclonal Gammopathy of Undetermined Significance, 164 J. Neurol. Sci. 64 (1999).

[18] Charlene McShane et al., Prior Autoimmune Disease and Risk of Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma: A Systemic Review, 23 Cancer Epidemiol. Biomarkers Prev. 332 (2014).

specific causal relationship between any autoimmune disease and the development of a monoclonal gammopathy or multiple myeloma. Pet. Ex. 31, Tab M at 335, 340. The article thus concludes only that the two conditions "may be of autoimmune origin" and that "immune-based biomarkers may be useful in predicting disease onset and progression." Id. at 340.

Finally, Dr. Latov referenced the Soderberg study. Tr. 30; see Pet. Ex. 31, Tab W.[19] Dr. Latov posited that the authors in Soderberg concluded that chronic autoimmunity and immune stimulation could contribute to the development of hematological malignancies or myeloma. Tr. 30. Indeed, Soderberg studied roughly 40,000 cases of leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, and myeloma in Sweden during 1987-1999 to investigate potential associations between several autoimmune diseases. Pet. Ex. 31, Tab W at 3028. Researchers in Soderberg found an elevated risk of malignancy in autoimmune haemolytic anemia and idiopathic thrombocytopenic purpura. Id. They theorized that chronic autoimmunity or immune stimulation induced by activated immune cells could lead to random mutation in dividing cells. Id. at 3028. Although petitioner in the present matter was not diagnosed with a preceding autoimmune disorder, Dr. Latov maintained that the Soderberg article supported his opinion given that monoclonal gammopathies are thought to precede the development of myeloma. Tr. 31.

All in all, Dr. Latov agreed that there is "no proof" that GBS/CIDP can contribute to the development of POEMS syndrome, but he continued to maintain that evidence of a temporal relationship between the two suggests petitioner's POEMS could be due to chronic immune stimulation. Tr. 30. Given the rarity of the disease, Dr. Latov acknowledged that he knew of no study detailing any direct relationship between GBS/CIDP and POEMS. Tr. 40. Dr. Latov thus relied upon case reports to establish a causal link between GBS and/or CIDP and POEMS syndrome. Id.

The first case report cited by Dr. Latov was the Sojka case report. See Pet. Ex. 29, Tab Q. On cross examination, respondent maintained that the Sojka case report described a patient who presented with GBS-like symptoms, but ultimately received a POEMS diagnosis following testing which confirmed the presence of the monoclonal protein. Tr. 40-42; Pet. Ex. 29, Tab Q at 284. Respondent posited that the patient was diagnosed with GBS at onset due to the similarity in neuropathy-related features as well as the initial negative testing for the monoclonal protein. Tr. 40-42. Dr. Latov proposed, however, that the patient likely had GBS initially and developed POEMS months later, consistent with his theory that the chronic inflammation associated with GBS can result in POEMS. Tr. 42.

Dr. Latov also commented on the Isose article, a case report and review of thirty POEMS cases. Tr. 74; see Resp. Ex. A, Tab 6 at 678. The case report discussed in Isose describes a patient who presented initially with acute neuropathy symptoms thought to be related to GBS and then CIDP following a six-week progression of symptoms. Resp. Ex. A, Tab 6 at 678. A laboratory examination conducted around six weeks after onset was positive for monoclonal gammopathy. Id. The patient was thereafter diagnosed with POEMS around eight weeks

[19] Karin Soderberg et al., Autoimmune Diseases, Asthma and Risk of Hematological Malignancies: A Nationwide Case-Control Study in Sweden, 42 Eur. J. Cancer 3028 (2006).

following the onset of her neuropathy after additional laboratory results revealed elevated serum VEFG levels. Id. Dr. Latov maintained that the patient described in Isose suffered from GBS and POEMS "concurrently[,]" as the POEMS syndrome diagnosis occurred multiple weeks after the neurological abnormalities were recorded. Tr. 74.

As to the timing of onset of R.S.'s illness, Dr. Latov maintained that she experienced her first symptom of GBS two weeks post vaccination. Tr. 33. In his view, a two- week onset falls within an appropriate timeframe for an immune-mediated injury caused by a vaccine. Id. For support, Dr. Latov relied primarily on the flu/GBS epidemiologic evidence in the Schonberger study. As discussed earlier, researchers in Schonberger studied the incidence of onset of GBS following the swine flu vaccine, concluding that an increase in disease frequency occurred mostly within a five-week week period thereafter. Pet. Ex. 29, Tab P at 105.

To conclude, Dr. Latov briefly addressed evidence in the record suggesting R.S. suffered from some gastrointestinal infection three days following her receipt of the flu vaccine in October 2013. Tr. 70. Dr. Latov acknowledged that prior infection can be a precursor illness to GBS, but he felt petitioner's illness was too mild to be causal given that she did not experience accompanying systemic manifestations such as a fever. Tr. 70-71. Even so, Dr. Latov theorized that a pre-existing gastrointestinal infection, coupled with a vaccination, could combine to trigger GBS. Tr. 71.

ii. Samir Parekh, M.D.

Dr. Parekh served as petitioner's second testifying expert. He offered one expert report in support of her claim. See Pet. Ex. 57. Consistent with Dr. Latov, Dr. Parekh offered the opinion that R.S. initially presented with GBS in November 2013, and that chronic immune stimulation produced secondarily to GBS caused R.S. to develop POEMS syndrome thereafter in August 2014. Tr. 225, 249-50, 251.

Dr. Parekh received his medical degree from the K.J. Somaiya Medical College at the University of Bombay in India. Tr. 213. After medical school, Dr. Parekh completed an internship and residency in internal medicine at Rush University in Chicago, Illinois. Id. He thereafter completed a clinical and research fellowship in hematology and medical oncology at Albert Einstein College of Medicine in New York. Id. In his clinical fellowship, Dr. Parekh treated patients with a variety of cancer and non-cancer hematological diseases. Id. He trained specifically in bone marrow transplantation. Tr. 214.

Dr. Parekh is board certified in internal medicine and hematology. Tr. 214. Following his university training, he worked as an Assistant Professor at the Albert Einstein College of Medicine from 2003 to 2013. Id. At present, he serves as an Associate Professor of Hematology and Oncology, with a secondary appointment in oncological sciences within the graduate school, at the Icahn School of Medicine at Mount Sinai Medical Center. Tr. 215. As part of his research duties, Dr. Parekh studies the genomics of multiple myeloma. Tr. 216-17. His lab work also includes drug development for myeloma and hematological malignances. Id. Dr. Parekh also

attends to patients in a clinical setting, focusing on hematological malignances and myelomas. Id. He has treated and diagnosed individuals with POEMS syndrome. Tr. 219.[20]

Dr. Parekh's opinion largely mirrored Dr. Latov's although Dr. Parekh delved further into the debate regarding the proper diagnosis of petitioner's symptoms, whether GBS and POEMS, *or* solely POEMS. Dr. Parekh began by discussing the underlying components of plasma cell dyscrasias. Tr. 223. He defined plasma cell dyscrasias as a spectrum of diseases caused by an over production of abnormal plasma cells clones. Id. Dr. Parekh explained that healthy individuals produce plasma cells, a type of disease-fighting white blood cell, which make antibodies against the various foreign antigens entering the body. Id. In patients with plasma cell dyscrasia, the plasma cell starts reproducing uncontrollably, making copies of itself and producing an excess of the antibody or immunoglobulin. Id. The most common plasma cell disorder is the monoclonal gammopathy of unknown significance or "MGUS[,]" a term used to describe a patient that has an abnormal blood test showing a protein of clonal nature. Tr. 224. As the plasma cells continue to grow in excess, they can result in low blood counts, kidney failure, bone lesions, or in severe cases, active myeloma. Tr. 224-25.

Dr. Parekh next discussed the four diagnostic criteria for a POEMS syndrome diagnosis, as described in the Dispenzieri article. Tr. 225; Pet. Ex. 57 at 3; see Pet. Ex. 29, Tab F at 215. The Dispenzieri article categorizes the two main criteria as monoclonal plasma cell disorder and neuropathy. Tr. 226. The third criteria for POEMS syndrome must consist of one of the following: elevated VEGF, the presence of Castleman's disease, or sclerotic lesions. Id. The final criteria encompass multiple "minor criteria" and can include organomegaly, endocrinopathy, skin changes, papilledema, thrombocytosis, and others. Tr. 226-27.

Based on his review of what he deemed the appropriate clinical criteria, Dr. Parekh opined that R.S. had been correctly diagnosed with POEMS syndrome. Tr. 227. As he explained, she presented with a polyneuropathy in 2013 and thereafter developed a monoclonal plasma cell disorder, elevated VEGF, raised intracranial tension, and papilledema. Id. In his assessment of the contemporaneous medical record, Dr. Parekh's discussion of R.S.'s clinical course focused primarily on the hematologic aspects of the disease. He mostly deferred to Dr. Latov to explain the significance of her polyneuropathy and presumed GBS diagnosis in November 2013, but he did offer some testimony regarding her early symptoms. Id.

Dr. Parekh maintained that R.S.'s initial neuropathy symptoms were more consistent with a GBS. Tr. 246-47. In support, Dr. Parekh posited that petitioner experienced a neuropathy characterized by "ascending neurological deficit[,]" which he considered more indicative of GBS. Tr. 247. Dr. Parekh also referenced petitioner's cranial nerve involvement (i.e., drooling), occurring at initial onset. Dr. Parekh testified that patients with POEMS syndrome typically do not experience symptoms indicative of cranial nerve disfunction. Tr. 231. He otherwise deemed the symptom to be neurological in nature and deferred to Dr. Latov's interpretation regarding its significance. Id. Dr. Parekh also noted that multiple of R.S.'s treaters assessed her with GBS and associated the condition with the flu vaccine. Tr. 242-43.

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[20] On cross examination, Dr. Parekh confirmed that he does not diagnose patients with GBS. Tr. 242.

Dr. Parekh also briefly referenced petitioner's initial response to IVIG therapy following her hospital presentation for neuropathy symptoms. Tr. 247; Pet. Ex. 57 at 3. Consistent with Dr. Latov, he posited that a positive response to IVIG would be consistent with a GBS neuropathy. Tr. 247. Dr. Parekh acknowledged on cross examination, however, that he was aware of case reports showing patients with POEMS syndrome can respond well to IVIG therapy. Id.

Dr. Parekh otherwise discussed at length the evidence in petitioner's medical record which he deemed best supportive of an onset of POEMS syndrome. He began by explaining the significance of Ms. Saver's SPEP tests in relation to her development of a monoclonal gammopathy. Tr. 227. Consistent with the medical record, Dr. Parekh noted that R.S.'s initial SPEP test, conducted without immunofixation, in November 2013 was negative for M- protein. Tr. 228, 248-49; see Pet. Ex. 5 at 826. A second SPEP test from February 2014 revealed two IgA lambda M-components of .22 grams per deciliter and .06 grams per deciliter, respectively, in the beta region. Tr. 228, 248-49. Based on his reading of R.S.'s February 2014 test, Dr. Parekh posited that she had an abnormal plasma clone at that time. Tr. 228, 249; see Pet. Ex. 57 at 5.

By August 2014, R.S. had elevated VEGF, thereby satisfying the third clinical criteria of POEMS syndrome. Tr. 228. Petitioner also underwent a bone marrow biopsy in mid- August, showing a small clonal IgA-positive plasma cell population in the marrow. Tr. 228-29; see Pet. Ex. 18 at 1049. As Dr. Parekh explained, healthy individuals have up to five percent of polyclonal plasma cells, that is cells having both kappa and lambda light chains. Tr. 229-30. R.S.'s biopsy results revealed an abnormal lambda light chain restriction in five percent of her cells, which further supported a finding of monoclonal gammopathy. Tr. 230.

On cross examination, Dr. Parekh discussed the relevancy of petitioner's active thrombocytosis and its relationship to POEMS syndrome. Tr. 244-46. As noted earlier, R.S. presented with elevated platelet levels during her initial hospitalization in November 2013. Tr. 244. Dr. Parekh acknowledged this symptom, but categorized the findings as nonspecific in the context of a POEMS diagnosis. Tr. 244-45; see also Pet. Ex. 57 at 4-5. As he explained, thrombocytosis is a common occurrence in response to unspecified inflammation, infection, or iron deficiency/anemia. Tr. 245-46. Concerning POEMS syndrome, he agreed that thrombocytosis could be a minor finding associated with the illness. Tr. 246.[21] Dr. Parekh maintained, however, that elevated platelets are not specific enough to diagnosis a patient with POEMS. Id.

Based on the findings discussed above, Dr. Parekh opined that R.S. met the diagnostic criteria for POEMS in or around August 2014. Tr. 231, 249-50. Once diagnosed, she started Revlimid, along with dexamethasone for four cycles, followed by an autologous stem cell transplant, and responded well to both therapies (i.e., her VEGF levels decreased). Tr. 232. Along those same lines, Dr. Parekh acknowledged that R.S. responded somewhat to IVIG

[21] Dr. Parekh also agreed that R.S.'s thrombocytosis remained persistent throughout her illness and resolved following treatment for POEMS. Tr. 245-46.

therapy in the early stages of her illness. Id. In his clinical experience, however, Dr. Parekh explained that IVIG is not the typical treatment of choice for POEMS syndrome, given that IVIG is not directed at eradicating the plasma cell clone. Id. Nonetheless, Dr. Parekh acknowledged that POEMS may respond to IVIG is some instances. Id. ("there are anecdotal examples where POEMS may respond").

Dr. Parekh next offered his own interpretation of the medical theory of causation applicable herein. Consistent with Dr. Latov, Dr. Parekh opined that the chronic immune stimulation, resulting secondarily from a GBS diagnosis, caused R.S. to develop an overabundance of plasma cells, which in turn led to her onset of POEMS syndrome. Tr. 232, 240-41. To connect chronic immune stimulation and plasma cell dyscrasia, Dr. Parekh began by explaining how plasma cells develop in the body. Tr. 232-33. Plasma cells originate as immature B cells in the bone marrow. Id. Following formation, immature B cells are released into the bloodstream, exposing them to various foreign antigens. Tr. 232-33. B cells then enter the lymph nodes, where they undergo several rounds of a maturation process called high affinity antibody selection to learn how to make antibodies to a particular antigen. Tr. 233. The maturation process produces two types of cells: plasma cells and memory B cells. Id. The remaining cells are deleted from the system via apoptosis. Id.

Along those same lines, Dr. Parekh posited that antigens can also be important in the developed of plasma cell proliferation. Tr. 233. In reference to the maturation process discussed above, Dr. Parekh opined that B cells, when presented to an antigen, can become "malignant and undergo monoclonal expansion near the population of expanded cells." Tr. 235. For support, Dr. Parekh referenced the Nair article. Id. at 233-34, 312-13; see Pet. Ex. 61.[22] Nair examined the clonal immunoglobulin in Gaucher's patients and in mouse models of Gaucher's disease-associated gammopathies to determine if long-term immune activation could stimulate the monoclonal gammopathy associated with the disease.[23] Tr. 234. Researchers in Nair determined that the monoclonal protein underlying the disease-associated gammopathy is specific for certain lysolipids (LGLI and LPC). Id.; see Pet. Ex. 61 at 555. Taken together, Dr. Parekh posited that these proteins could cause the body to develop an overabundance of plasma cells. Tr. 234. Researchers in the same study also conducted experimental mouse models and determined that Gaucher's medication could reduce the effect of monoclonal protein spikes in gammopathy patients. Id. Dr. Parekh suggested that this finding further supported his suspicion that removing "the antigen" causes plasma cell proliferation to resolve. Id.

Dr. Parekh also suggested that cytokines, specifically the IL-6 variant, can stimulate plasma cell growth. Tr. 235. Dr. Parekh referenced the Rush article in support of this assertion. Tr. 235-36. In Rush, researchers conducted a mouse model study to determine if IL-6 can cause plasma cell dyscrasia. Tr. 236. As part of their experiment, the authors genetically engineered mice to overexpress IL-6 and determined that mice injected with the substance developed an

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[22] Shiny Nair et al., Clonal Immunoglobulin Against Lysolipids in the Origin of Myeloma, 374 New Eng. J. Med. 555 (2016).

[23] Dr. Parekh defined Gaucher's disease as an inborn error of metabolism where patients are deficient in a particular enzyme. Tr. 234.

increase in plasma cells and tumors. Id. Dr. Parekh posited that cytokines can also stimulate an overgrowth of myeloma cells, as well as further cytokine expansion, resulting in a "vicious circle of self-perpetuating growth." Tr. 236-37. Dr. Parekh explained that VEGF, an element strongly considered to be pivotal to the pathogenesis of POEMS syndrome, is a cytokine secreted by plasma cells that causes blood vessel leakage. Tr. 237, 311-12; see Pet. Ex. 29, Tab F at 215.

Dr. Parekh next went on to discuss the mineral oil plasmacytoma model or "MOPC[,]" an experimental mouse model he deemed instrumental in studying the development of plasma cell disorders. Tr. 238-39; see Pet. Ex. 68;[24] Pet. Ex. 60.[25] The Potter article indicates that the mineral oil, pristane, can stimulate plasma cell growth in mice by irritating the peritoneal cavity. Tr. 238; see Pet. Ex. 68 at 18, 28-31. Similarly, researchers in Hofgaard used the same technique to test a multiple myeloma model suitable for studying bone marrow tropism, development of osteolytic lesions, drug testing, and immunotherapy. Pet. Ex. 60 at e51892. According to Dr. Parekh, these two studies support his opinion that a "chronic irritating stimulus can cause inflammation leading to plasma cell dyscrasia." Tr. 238-39.

Finally, Dr. Parekh referenced the Lindqvist epidemiologic study. Tr. 239; Pet. Ex. 59. Lindqvist is a case-controlled study of both monoclonal gammopathy (21,0000 controls/5,000 diagnoses) and myeloma patients (75,000 controls/19,0000 diagnoses), which analyzed the relationship between autoimmune disease and risk of developing plasma cell dyscrasia. Pet. Ex. 59 at 6284. Dr. Parekh referenced table two in the article, which lists multiple autoimmune conditions including GBS, as possibly associated with both monoclonal gammopathy and multiple myeloma. Id. at 6286. The article reports that 6/8 patients developed GBS following onset of a monoclonal gammopathy. Id. Dr. Parekh understood this study to support "an increased risk of developing [monoclonal gammopathy] of almost three-fold." Tr. 239, 252-53. Notably, the article does not discuss the relationship between autoimmune disease and POEMS syndrome. Tr. 253.

Apart from the articles referenced above, Dr. Parekh could not recall any medical literature or evidence to suggest that GBS can be a precursor illness to POEMS, or any other literature directly connecting GBS to POEMS syndrome. Tr. 251.

iii. Brea Lipe, M.D.

Respondent's first expert, Dr. Lipe, prepared two expert reports and testified at hearing. See Resp. Exs. C, E. She proposed that R.S. was properly diagnosed with POEMS syndrome beginning in October/November 2013 with her initial onset of neuropathy. In addition, Dr. Lipe posited that the flu vaccine played no role in her development of the condition.

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[24] Michael Potter, The Early History of Plasma Cell Tumors in Mice, 1954-1976, 98 Advances Cancer Res. 17 (2007).

[25] Peter Hofgaard et al., A Novel Mouse Model for Multiple Myeloma (MOPC315.BM) That Allows Noninvasive Spatiotemporal Detection of Osteolytic Disease, 7 PolsOne e51892 (2012).

Dr. Lipe obtained her bachelor's degree from the University of Colorado. Tr. 255; see Resp. Ex. D at 1. Thereafter, she attended medical school at Albany Medical College. Tr. 255. She completed her residency, followed by a fellowship in hematology and oncology at Dartmouth-Hitchcock Medical Center. Id. She then went on to receive a master's degree in clinical research from the University of Kansas. Tr. 255. Dr. Lipe is board-certified in hematology and internal medicine. Tr. 256. At present, Dr. Lipe serves as an Associate Professor and the Director of Clinical Myeloma at the University of Rochester, where she treats patients suffering from a wide range of plasma cell disorders. Tr. 255-56. She also oversees clinical trials and research on topics including multiple myeloma and monoclonal gammopathies. Tr. 257. As part of her clinical practice, Dr. Lipe estimated that she has diagnosed roughly ten to fifteen patients with POEMS syndrome over the course of her career. Tr. 259. She is also part of a working group with the College of American Pathology that is working to create guidelines for diagnosing monoclonal gammopathies. Tr. 257.

Dr. Lipe began by discussing POEMS syndrome and the diagnostic criteria relevant to the condition. Tr. 260. Dr. Lipe defined POEMS syndrome as a hematologic disease of the plasma cells, or a "plasma cell dyscrasia." Tr. 263, 289; see also Resp. Ex. C at 3. Consistent with the testimony offered by petitioner's experts, Dr. Lipe cited literature discussing the criteria required for diagnosis, which includes both a polyneuropathy and plasma cell clone or monoclonal gammopathy, and one of the following: VEGF elevation, sclerotic bone lesions, or Castleman's disease. See Resp. Ex. C, Tab 3 at 2496.[26] Other minor criteria can include papilledema, thrombocytosis, skin changes, and organomegaly. Id. Dr. Lipe estimated the frequency of a POEMS diagnosis to be 1 in 330,000. Tr. 261.

Based on her clinical experience and review of the medical literature, Dr. Lipe opined that patients with POEMS syndrome typically present with related symptoms nine to sixteen months prior to diagnosis. Tr. 262; see Resp. Ex. C, Tab 4 at 304. The initial onset of symptoms, however, can present acutely, causing rapid deterioration within two weeks at the earliest. Tr. 268. Overall, Dr. Lipe maintained that patients with POEMS syndrome do not present with every possible symptom all at once. Tr. 287. Rather, over time, POEMS patients accumulate more of the features of the syndrome. Id.

Dr. Lipe further posited that POEMS syndrome is often times initially misdiagnosed as CIDP or AIDP, conditions similar to GBS. Tr. 260-61, 282, 293; see Resp. Ex. E at 1. For support, Dr. Lipe referenced the Nasu and Dispenzieri articles. Tr. 261. Nasu analyzed over one hundred patients diagnosed with POEMS and CIDP to elucidate the differences in the neuropathy profiles of both diseases. See Resp. Ex. E, Tab 1 at 476. The authors in Nasu reported that sixty percent of POEMS syndrome patients were initially diagnosed with CIDP following an onset of polyneuropathy. Tr. 261; Resp. Ex. E, Tab 1 at 477. Similarly, researchers in Dispenzieri concluded that eighty-five percent of patients with POEMS syndrome were commonly misdiagnosed with AIDP or CIDP. Tr. 261; see Resp. Ex. C, Tab 3.

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[26] Angela Dispenzieri et al., POEMS Syndrome: Definitions and Long-Term Outcome, 101 Blood 2496 (2003).

Dr. Lipe stated that patients who are initially misdiagnosed are not considered to still be suffering from GBS/CIDP/AIDP once the POEMS diagnosis is made. Tr. 261. Indeed, Dr. Lipe reported that she has treated POEMS patients who are misdiagnosed at onset, but none who have distinct GBS/CIDP either consecutively or simultaneous with POEMS. Tr. 262. She also testified that she was not aware of any literature or evidence to suggest the conditions are linked in any way. Id. In so stating, Dr. Lipe offered her own interpretation of the case reports of GBS followed by onset of POEMS submitted by petitioner's experts. For instance, Dr. Lipe classified the Sojka case report as a classic case of misdiagnosis. Tr. 262.

Dr. Lipe next discussed the medical records filed in the present matter in relation to her opinion regarding petitioner's onset of POEMS syndrome. Tr. 264. Dr. Lipe posited that R.S.'s POEMS presentation was typical compared to those she has treated in the past. Tr. 267. In reference to the medical record, Dr. Lipe stated that petitioner reported to the emergency room initially with thrombocytosis and neuropathy-related symptoms in late November 2013. Tr. 282. Her course thereafter continued to deteriorate over an eight-month period. By July and August 2014, VEGF levels were drawn[27] and SPEP testing with immunofixation confirmed the presence of the monoclonal protein. Tr. 284-85. Based on the above, Dr. Lipe did not dispute that R.S. was officially diagnosed with POEMS syndrome in August 2014. Id. She maintained, however, that the diagnosis and biologic onset of the condition are two distinct events. Tr. 281.

Given her overall course, Dr. Lipe posited that R.S.'s onset of neuropathy in October/November 2013 constituted the onset of her POEMS syndrome. Tr. 282; Resp. Ex. C at 4. In support, Dr. Lipe cited to medical literature which differentiated between neuropathies associated with POEMS from those with GBS/CIDP. Tr. 283; see, e.g., Resp. Ex. C, Tab 4 at 304. Dr. Lipe posited that POEMS-associated neuropathies are routinely accompanied by pain and edema,[28] unlike those attributable to GBS/CIDP. Tr. 284, 293. As Dr. Lipe noted, petitioner's records documented initial complaints of pain and lower extremity edema during her initial hospitalization in November 2013. Id.

Moreover, Dr. Lipe referenced petitioner's medical visit at the Mayo Clinic, with Dr. Dispenzieri, as supportive evidence of an onset of POEMS disease in October 2013. Tr. 285. Indeed, Dr. Dispenzieri placed onset of petitioner's POEMS in 2013, at which time she experienced neuropathy-related symptoms, fatigue, and a cherry angioma eruption. Pet. Ex. 19 at 27. As Dr. Lipe recalled, Dr. Dispenzieri did not entertain GBS or CIDP as an alternative or concurrent diagnosis or cause. Id. Given her knowledge of the disease, Dr. Lipe gave Dr. Dispenzieri's opinion a great deal of weight when formulating her opinion. Id. ("[Dr. Dispenzieri] is probably the world's expert in diagnosis of POEMS" in the United States.).

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[27] On redirect examination, Dr. Lipe stated that there is no way to determine how long R.S.'s VEGF was elevated prior to August 2014. Tr. 314. Had the VEGF test been conducted in November 2013, Dr. Lipe speculated that it would have been positive at that time. Tr. 315.

[28] Dr. Lipe posited that edema is a postulated mechanism by which POEMS patients develop neuropathy. Tr. 315.

Next, Dr. Lipe discussed petitioner's thrombocytosis diagnosis and its relevance to her condition. Tr. 265-66. In general, Dr. Lipe agreed that thrombocytosis can be a nonspecific finding when taken in isolation. Tr. 266. In R.S.'s case, however, Dr. Lipe attributed her onset of thrombocytosis in November 2013, and overall persistence through August 2014, to POEMS syndrome. Tr. 266. Dr. Lipe posited that transient or reactive-type thrombocytosis would resolve on its own over time. Thrombocytosis attributable to POEMS syndrome, however, would not improve until the patient's underlying plasma cell disorder was treated. Id. Consistent with the medical records filed herein, Dr. Lipe noted that R.S.'s thrombocytosis did not improve until her physicians definitively treated her for POEMS in 2014. Tr. 266-67; see Resp. Ex. E at 1-2.

Dr. Lipe also posited that petitioner's subsequent development of an abnormal increase in cherry angiomas in mid-2014 was attributable to POEMS syndrome. Tr. 286; see Pet. Ex. 3 at 5, 12, 16. Dr. Lipe acknowledged that petitioner may have had some history of cherry angiomas prior to her onset of the disease, which she deemed unrelated to the condition. Tr. 286-88. The increase to two angiomas in April 2014 and seven in May 2014, however, would be consistent with angiomas related to POEMS syndrome. Tr. 287-88.

Consistent with the testimony offered by petitioner's experts, Dr. Lipe opined that cranial nerve involvement or facial nerve involvement (i.e., drooling) is not typically seen in POEMS syndrome. Tr. 267. Dr. Lipe could not recall treating a patient with facial nerve symptoms specifically. Id. In her own clinical practice, Dr. Lipe stated that she has treated POEMS patients who experienced pulmonary and swallowing difficulties. Tr. 267. Based on her clinical experience, Dr. Lipe posited that petitioner's initial respiratory complaints were best attributable to POEMS syndrome. Tr. 267. She could not, however, definitively relate petitioner's drooling to POEMS given the lack of support relating facial nerve symptoms to the condition. Id.

Dr. Lipe next offered her interpretation of petitioner's SPEP testing over the course of her illness. Tr. 268. As discussed by petitioner's experts on direct examination, R.S.'s initial SPEP testing from November 2013 was negative for M-protein. Tr. 268. As Dr. Lipe noted, however, the initial test did not include immunofixation, the method by which the M-protein could be detected, meaning there was no way of knowing if she had a monoclonal gammopathy at that time. Tr. 268-69. R.S.'s subsequent SPEP in February 2014, which was conducted with immunofixation, confirmed the presence of monoclonal protein. Tr. 269.

Given that the 2013 SPEP test was conducted without immunofixation, Dr. Lipe acknowledged that she could not say for certain if petitioner would have tested positive for monoclonal protein at that time. Tr. 269. She suspected, however, that if the immunofixation had been conducted, it likely would have been positive. Tr. 271. Moreover, Dr. Lipe opined that petitioner's November 2013 SPEP test revealed an abnormal beta peak. Tr. 270; see Pet. Ex. 5 at 770-71. Dr. Lipe acknowledged that petitioner's treaters documented the testing as normal, but she interpreted the abnormal beta spike as a cause for concern. Tr. 270, 305; see Resp. Ex. C, Tab 9 at 106.[29]

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[29] Theodore O'Connell et al., Understanding and Interpreting Serum Protein Electrophoresis, 71 Am. Fam. Physician 105 (2005).

Dr. Lipe next discussed petitioner's initial response to IVIG treatment. Tr. 264. Based on her review of the relevant literature, Dr. Lipe agreed that the majority of patients with POEMS syndrome do not respond well to IVIG therapy. Id. She noted, however, that there are case reports where patients do respond to IVIG. Id. In addition, Dr. Lipe posited that the underlying neuropathy associated with POEMS is traditionally treated with IVIG, thus many patients can experience an improvement of symptoms initially. Id. In R.S.'s case, Dr. Lipe agreed that the IVIG therapy she received in late November 2013 and continuing through early 2014 resulted in some benefit to her condition. Tr. 294. Overall, however, Dr. Lipe posited that petitioner's health continued to deteriorate and her physical exams did not improve to the same degree following subsequent treatment. Id. In her view, the fundamental biology of her disease did not change based on the treatment course. Id.

Along those same lines, Dr. Lipe opined that petitioner's initial treatment with Solu-medrol could have played some role in her resolution of symptoms following her first hospital admission. Tr. 264, 294; Resp. Ex. E at 2. Dr. Lipe referenced the Dispenzieri article in support, which indicated that fifty percent of patients with POEMS syndrome respond to steroid therapy. Tr. 265, 296; see Resp. Ex. C, Tab 3 at 2501. Dr. Lipe acknowledged that R.S.'s initial improvement was attributed to IVIG, though she felt that it was possible that the Solu-medrol played a relevant part in her initial improvement. Tr. 265. Moreover, Dr. Lipe noted that petitioner did not receive steroid treatment during her second and third hospitalizations at which time her response to treatment was less robust. Id.

Moving forward, Dr. Lipe commented on the medical theory of causation proffered by petitioner's experts. Given her understanding of plasma cell biology, Dr. Lipe firmly disagreed that chronic immune stimulation is an accepted pathogenic mechanism for the development of plasma cell dyscrasia. Tr. 271, 277; see Resp. Ex. C at 6-7; Resp. Ex. E at 3-4. She knew of no medical literature or case reports supporting petitioner's theory that immune stimulation occurring secondarily due to GBS or CIDP could cause POEMS. Tr. 272.

Overall, Dr. Lipe posited that the literature submitted by petitioner in support of her theory focused heavily on conditions distinguishable from POEMS. The Lindqvist paper, for example, analyzed 5,403 patients with monoclonal gammopathy of unknown significance and multiple myeloma (compared to 21,209 controls) to determine if autoimmune diseases increase the risk of developing either condition. Tr. 273-75. Dr. Lipe gave little weight to the Lindqvist paper due to its structure. Tr. 273 ("epidemiologic studies, particularly MGUS, the way this was done, is particularly problematic"), 298-99. As she explained, monoclonal gammopathies of unknown significance are asymptomatic; thus, they are only detected once some other disease process has triggered adverse symptoms. Id. In her review of Lindqvist, Dr. Lipe noted that selection criteria for the study was limited to monoclonal gammopathy of unknown significance only, and did not account for any underlying disease process the patients might have experienced contemporaneously.

Dr. Lipe otherwise categorized any association between monoclonal gammopathy and GBS to be too speculative. Tr. 275. In support, Dr. Lipe again referenced the Lindqvist study. Based on their findings, the Lindqvist authors reported that six patients with monoclonal

gammopathy had concurrent GBS out of roughly 26,000 total case test participants. Tr. 275. Dr. Lipe agreed that the Lindqvist article reported an elevated odds ratio of GBS in MGUS patients, but she maintained that such a small number does not suggest evidence of pathogenesis regarding monoclonal gammopathies. Tr. 276, 297. Moreover, Dr. Lipe critiqued the study for aggregating results. Tr. 276-77. As she explained, the study broadly concludes that autoimmune diseases are associated pathologically with monoclonal gammopathies based on multiple different conditions. Id. In her view, articles like Lindqvist, McShane, Soderberg, and Shimanovsky (see Pet. Ex. 31, Tab V),[30] amount to low statistical significance. Tr. 276-77, 298-301.

Similarly, Dr. Lipe attributed little weight to the mouse model evidence offered by petitioner's experts to support their chronic immune stimulation theory. Tr. 277. Dr. Lipe posited that the mouse model experimentation, as it relates to monoclonal gammopathies and multiple myeloma, offered by petitioner does not prove that immune stimulation can cause plasma cell dyscrasia. Tr. 278. Dr. Lipe explained that monoclonal gammopathies and myeloma do not occur naturally in mice. Tr. 277-78. Thus, mice populations used in myeloma studies have been repeatedly inbred, resulting in internal genetic manipulation. Tr. 278. Based on her review of the studies submitted, Dr. Lipe could not agree that lipid stimulation in mice and a resulting production of plasma cells supports a conclusion that immune stimulation can cause myeloma in humans. Tr. 278.

Dr. Lipe also critiqued petitioner's attempt to relate literature discussing Gaucher's disease and onset of monoclonal gammopathies to plasma cell dyscrasia induced by chronic immune stimulation. Tr. 279. Dr. Lipe agreed with the underlying biology presented in Nair as explained by petitioner's experts to show how plasma cells develop in response to foreign antigens. Tr. 279. As discussed in Nair, researchers studied the capacity of certain lysolipids to mediate B-cell activation and serve as antigenic targets in Gaucher's-associated monoclonal gammopathies. Pet. Ex. 61 at 555, 560. Dr. Lipe found the paper to be helpful in assessing how best to treat gammopathies associated with the disease. Tr. 279-81. As she explained, lysolipids associated with Gaucher's are abnormal proteins produced by abnormal cells. Dr. Lipe thus stressed that a target antigen is not always pathogenic or causative, meaning that targets as referenced in Nair could more be symptom-like, occurring as a result of some other mechanism related to the disease process, but treatable in the long term. Tr. 280. Based on her own review of the article, Dr. Lipe could not conclude that antigen stimulation could cause a plasma cell mutation. Tr. 281.

When questioned further regarding her own understanding of POEMS syndrome and its pathogenesis, Dr. Lipe stated that she could not identify a specific causal mechanism given the state of the research at present. Tr. 290. Dr. Lipe opined that many researchers believe that proinflammatory cytokines, IL-1, IL-6, and VEGF in particular, could play some role in the

[30] The authors in Shimanovsky reported that patients with preexisting autoimmune conditions have a higher prevalence of monoclonal gammopathy of undetermined significance and multiple myeloma. Alexei Shimanovsky et al., Autoimmune Manifestations in Patients with Multiple Myeloma and Monoclonal Gammopathy of Undetermined Significance, 6 BBA Clinical 12, 12 (2012).

condition's development. Tr. 290, 301, 304. For instance, Dr. Lipe referenced the Gherardi article, which discussed the significance of IL-6 and its relationship to VEGF. Tr. 302-03; see Resp. Ex. C, Tab 1 at 1458.[31] In her review of Gherardi, Dr. Lipe agreed that IL-6 has been shown to be elevated in plasma cell dyscrasias, but she maintained that researchers do not known what role, if any, the elevation plays in the context of inflammatory diseases or plasma cell disorders. Tr. 303-04.

iv. Dennis Bourdette, M.D.

Respondent's second expert was Dr. Dennis Bourdette. He prepared one expert report and testified on behalf of respondent at the entitlement hearing. Tr. 88; see Resp. Ex. A. Consistent with Dr. Lipe, Dr. Bourdette proposed that R.S. was properly diagnosed with POEMS syndrome with onset in October/November 2013. In so stating, he refuted petitioner's assertion that she developed distinct GBS/CIDP in November, followed by POEMS syndrome the subsequent year. He opined that the flu vaccine petitioner received was unrelated to her diagnosis. Tr. 93.

Dr. Bourdette obtained his medical degree from the University of California at Davis. Tr. 89; see Resp. Ex. B at 1. He completed his internship at Santa Clara Valley Medical Center, followed by a three-year neurology residency at the VA Medical Center affiliated with Oregon Health and Science University ("OHSU"). Tr. 89. Dr. Bourdette is board-certified in neurology and holds an active medical license in Oregon. Id. He also currently serves as an article reviewer for the American Academy of Neurology's main publication, Neurology, as well as other sub-journals, including Neuroimmunology and Neuroinfection. Tr. 90. Dr. Bourdette has published over 200 peer-reviewed papers. Tr. 91.

At present, Dr. Bourdette serves as the Chairman of the Department of Neurology at Oregon Health and Science University. Tr. 89. He also directs the OHSU Multiple Sclerosis Center and Neuroimmunology Clinic. Id. In his clinical practice, he treats patients with various neuroimmunological conditions twice per week. Id. His current treatment specialty is Multiple Sclerosis. Id. at 90, 111.[32] Dr. Bourdette has also treated patients with GBS and CIDP over the course of his career. Tr. 90, 92. In addition, Dr. Bourdette testified that he has diagnosed at least one patient with POEMS syndrome. Tr. 91, 116-17. Over the years, he has also consulted on POEMS cases. Tr. 91.

Generally, Dr. Bourdette's testimony was consistent with Dr. Lipe's, although Dr. Bourdette's opinion focused largely on the debate regarding the proper onset of R.S.'s POEMS symptoms and any precursor illness she may have experienced. Based on his review of the accepted clinical criteria for POEMS syndrome, Dr. Bourdette agreed that petitioner was not officially diagnosed with the disease until early August 2014. Tr. 126-28. Based on his review

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[31] Romain K. Gherardi et al., Overproduction of Proinflammatory Cytokines Imbalanced by Their Antagonists in POEMS Syndrome, 87 Blood 1458 (1996).

[32] On cross examination, Dr. Bourdette acknowledged that he does not specialize in peripheral neuropathies. Tr. 111.

of the medical record, however, Dr. Bourdette opined that petitioner's subacute inflammatory neuropathy, which was originally diagnosed as idiopathic GBS, was her first manifestation of POEMS syndrome.[33] Tr. 94-95, 124, 135, 137; Resp. Ex. A at 3-4.

Based on his understanding of the literature, Dr. Bourdette posited that neuropathies associated with POEMS syndrome can present in both a rapidly progressive or slowly progressive manner. Tr. 116-18. In support of his opinion, Dr. Bourdette cited to case reports of patients with established POEMS syndrome, or within a few weeks or months of a neuropathy clearly had POEMS which was considered to be GBS-like at onset. Tr. 95, 129-31; see, e.g., Resp. Ex. A, Tab 10; Resp. Ex. A, Tab 4; Resp. Ex. A, Tab 1.[34]

In addition, Dr. Bourdette also cited to petitioner's various treatment records which analyzed her course retrospectively and placed onset of her illness in October/November 2013. Tr. 110. Following her POEMS diagnosis, Dr. Bourdette recalled that petitioner presented for an evaluation at the Mayo Clinic with Dr. Dispenzieri, a physician he deemed to be the world's leading expert in POEMS. Id.; see Pet. Ex. 19 at 27. Consistent with his review of petitioner's clinical course, Dr. Dispenzieri clearly attributed petitioner's 2013 neuropathy to POEMS. Tr. 110.

Dr. Bourdette took issue with petitioner's assertion that she suffered from acute GBS in November 2013, which then evolved into CIDP thereafter. Tr. 95, 118-19. He posited that CIDP can present in a variety of ways, including with an initial episode that looks like GBS initially, followed by a relapse of symptoms. Tr. 95-96, 132. Had petitioner not been diagnosed with POEMS syndrome, Dr. Bourdette stated that he would have diagnosed her with CIDP in retrospect, not acute GBS, given the she had an initial neuropathy with sequelae persisting for over two months. Tr. 96, 123-24. Consistent with Dr. Lipe's testimony, Dr. Bourdette agreed that POEMS syndrome can often be misdiagnosed as CIDP given the similarities in the presenting neurological symptoms. Tr. 98, 103, 118.

Dr. Bourdette also maintained that he knew of no reports of patients experiencing preexisting GBS/CIDP as a precursory illness, or concurrent CIDP, and POEMS. Tr. 129-31, 132-33, 134-35. In so stating, he refuted petitioner's assertion that the case report evidence filed in this case suggests that a POEMS patient can experience distinct GBS/CIDP prior to onset. Tr. 133-34; see, e.g., Pet. Ex. 29, Tab Q. Dr. Bourdette interpreted these case reports to conclude that POEMS symptoms can manifest with GBS or CIDP-like presentations, but he maintained that the authors clearly determined the early neurological symptoms were indicative of a POEMS diagnosis in retrospect. Tr. 134-35.

Dr. Bourdette posited that POEMS syndrome can also manifest as respiratory issues or lower cranial nerve dysfunction. Tr. 98-99. In support, Dr. Bourdette referenced the Allam

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[33] Dr. Bourdette relied on the Dispenzieri study to establish the accepted diagnostic criteria for POEMS. Tr. 125-26; see Pet. Ex. 31, Tab C.

[34] A. Abbas et al., A Case of POEMS Mimicking a Guillain-Barré Like Syndrome, 369 J. Neurol. Sci. 268 (2016).

article. Tr. 99-100; see Resp. Ex. H.[35] The authors in Allam conducted a symptom review of patients diagnosed with POEMS and found that roughly one third exhibited restrictive pulmonary function. Tr. 99. Five percent of patients were noted to have pulmonary issues secondary to the related neuropathy. Id. Furthermore, Dr. Bourdette cited to case report evidence indicating that speaking difficulties and issues with the lower cranial nerve can be attributable to POEMS. Tr. 100.

In his review of the medical record, Dr. Bourdette noted that petitioner experienced symptoms consistent with shortness of breath and voice irregularities/difficulty speaking at her initial hospital presentation in November 2013. Tr. 98-99. Dr. Bourdette categorized petitioner's respiratory problems as related to phrenic nerve dysfunction, while the voice symptoms were likely due to swallowing issues. Tr. 99. The instances of drooling noted in the record, Dr. Bourdette admitted, could be indicative of facial paralysis, but he maintained that those symptoms were likely attributable to swallowing difficulties as well. Id.[36] Dr. Bourdette posited that the lack of specificity in the contemporaneous record made it difficult to determine how petitioner's early treaters characterized the drooling abnormality. Tr. 99.

Dr. Bourdette also attributed petitioner's early diagnosis of thrombocytosis in November 2013 to be related to POEMS. Tr. 104, 119-20, 136-37; Resp. Ex. A at 4. In support, he referenced literature categorizing thrombocytosis as a minor criteria of the disease. Tr. 104. As Dr. Bourdette recalled, R.S. presented with elevated platelets counts at her initial hospital presentation in 2013, which persisted through August 2014 when she was diagnosed with POEMS. Tr. 104-05. Based on his review of the contemporaneous record, Dr. Bourdette posited that R.S.'s platelet levels did not return to normal until she was treated for POEMS syndrome. Tr. 104. He otherwise relied heavily on the opinion of petitioner's treating hematologists who related the thrombocytosis to an onset of POEMS syndrome in November 2013 around the time she also developed the neuropathy. Tr. 104-05. From a neurological standpoint, Dr. Bourdette opined that persistent thrombocytosis is not indicative of GBS. Tr. 105. He acknowledged that patients with GBS could have an initial rise in platelets levels during the acute phase of the disease, but any chronic platelet elevation would indicate a hematological problem. Id.

Consistent with Dr. Lipe, Dr. Bourdette opined that POEMS can also be associated with an increase in cherry angiomas. Tr. 105-06; Resp. Ex. A at 4-5. Dr. Bourdette recalled that at least one of petitioner's treaters reported that she experienced a significant increase in cherry angiomas as a part of her POEMS syndrome clinical course. Tr. 106. Based on his review of the medical record, however, Dr. Bourdette could not say for certain if the increases reported were

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[35] Joanne Allam et al., Pulmonary Manifestations in Patients with POEMS Syndrome, 133 Chest 969 (2008).

[36] On cross examination, Dr. Bourdette maintained that petitioner's records did not include persuasive evidence of complaints relating to lower facial numbness. Tr. 112-13; see Pet. Ex. 7 at 51. Dr. Bourdette explained that the numbness complaints in the record were reported by a nurse (at some point after her ER evaluation). Tr. 114. Based on his review of earlier records, he could not determine which treatment record confirmed this notation. Id.

well documented. Id. He also agreed with the testimony offered by Dr. Latov, characterizing cherry angiomas as common in the general population. Id. Regardless, Dr. Bourdette posited that the evidence of persistent thrombocytosis and the initial neuropathy were enough to establish an onset of POEMS in November 2013. Id.

Given petitioner's strong reliance on her initial improvement with IVIG treatment to establish that her neuropathy-related symptoms were indicative of GBS at onset, Dr. Bourdette spent some time discussing petitioner's treatment in the context of her overall course. Tr. 96. Dr. Bourdette acknowledged that petitioner had robust improvement following IVIG therapy during her first hospital admission.[37] Tr. 96, 115. Thereafter, she relapsed and received additional rounds of IVIG without the same robust improvement. Tr. 96. After a third treatment, Dr. Bourdette posited that petitioner's response was less improved, so overall, her symptoms clearly worsened over that period of time. Tr. 96-97, 115-16.

In addition, Dr. Bourdette explained that the medical literature on POEMS syndrome indicates that patients with POEMS can experience a transient improvement of symptoms following IVIG treatment. Tr. 97; Resp. Ex. A at 7; see Resp. Ex. A, Tab 10; Resp. Ex. A, Tab 1. He acknowledged, however, that it is well-accepted that IVIG is not a good or effective treatment for POEMS. Tr. 97, 116. Dr. Bourdette stated that he had not personally treated any POEMS patients with IVIG. Tr. 117. Even so, Dr. Bourdette did not accept this finding to be persuasive in establishing that R.S. had GBS at the onset of her illness especially when taken into context with her worsening course and eventual diagnosis. Tr. 97.

Dr. Bourdette next discussed the significance of petitioner's SPEP testing conducted over the course of her illness and its significance in determining the onset of POEMS. Tr. 100-03, 107-08. Consistent with Dr. Lipe and petitioner's experts, Dr. Bourdette recalled that R.S.'s SPEP test in November 2013, which was conducted without immunofixation, was interpreted as normal. Tr. 100, 121. The SPEP with immunofixation was not conducted until February 2014. Had the immunofixation and VEGF tests been conducted closer-in-time to her manifestation of neuropathy symptoms, Dr. Bourdette speculated that her contemporaneous treaters likely would have made the diagnosis of POEMS sooner. Tr. 107-08. Dr. Bourdette otherwise deferred to Dr. Lipe regarding the significance of the beta peak spikes seen in the her earlier SPEP tests and what those could have indicated at that time. Id.

Moving forward, Dr. Bourdette commented briefly on petitioner's medical theory of causation. Tr. 108. Consistent with Dr. Lipe, Dr. Bourdette stated that he knew of no literature linking vaccinations with POEMS syndrome or monoclonal gammopathies. Tr. 108-09; Resp. Ex. A at 6-7. Dr. Bourdette also knew of no case reports or literature suggesting that GBS/CIDP or the secondary immune stimulation produced as a result could cause POEMS with or without a preceding vaccination. Tr. 109, 138. Given the lack of supportive scientific literature associating GBS/CIDP with POEMS syndrome, Dr. Bourdette posited that petitioner's theory regarding vaccine causation was not well-supported. Tr. 109, 137-38. He otherwise did not dispute petitioner's assertion that the flu vaccine can cause GBS. Tr. 121, 124-25.

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[37] Dr. Bourdette also noted that petitioner received pain medication and physical therapy around this time, which could have played some role in her overall improvement. Tr. 135-36.

Dr. Bourdette deferred to Dr. Lipe on multiple topics related to plasma cell dyscrasias and the origins of monoclonal gammopathies. Tr. 121-22. On cross examination, he offered some further comments regarding the role of proinflammatory cytokines in the pathogenesis of POEMS syndrome. Tr. 122. Dr. Bourdette agreed that the relevant literature filed in this matter suggests that the proinflammatory cytokines have shown to be elevated in POEMS patients. Id. He posited that the IL-6 variant, specifically, can stimulate VEGF. Id. Even so, Dr. Bourdette maintained that cytokines have not been deemed a causal mechanism for POEMS. Tr. 123. In his view, speculation regarding the role of cytokines in the development of POEMS stems from the recognition that VEGF responds quite easily to therapy. Id.

VI. DISCUSSION

A. Legal Framework

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 & Human 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 & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). In particular, petitioner must prove that that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Id. at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

i. Causation

To receive compensation under the Program, petitioner must prove either: (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that she suffered an injury that was caused by a vaccination. See §§ 13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because petitioner does not allege that she suffered a Table injury, she must prove that the vaccine caused her illness. To do so, she must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and his injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury

("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and his injury ("Althen Prong Three"). § 13(a)(1); Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The causation theory must relate to the injury alleged. Thus, petitioner must provide a reputable medical or scientific explanation for her theory, although the explanation need only be "legally probable, not medically or scientifically certain," it must be "sound and reliable." Boatman v. Sec'y of Health & Human Servs., 941 F.3d 1351, 1360 (Fed. Cir. 2019); Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on 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 material contained 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' offered experts and rule in petitioner's favor when the evidence weighs in his favor. See Moberly, 592 F.3d at 1325-26 ("[f]inders 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).

ii. Law Governing Analysis of Fact Evidence

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. § 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." § 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such a determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993); Doe/70 v. Sec'y of Health & Human Servs., 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"); Rickett v. Sec'y of Health & Human Servs., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when

examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. Sanchez v. Sec'y of Health & Human Servs., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); Cucuras v. Sec'y of Health & Human Servs., 26 Cl. Ct. 537, 543 (1992), aff'd, 993 F.2d 1525 (Fed. Cir. 1993).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. Lowrie v. Sec'y of Health & Human Servs., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. Cucuras, 993 F.2d at 1528; see also Murphy v. Sec'y of Health & Human Servs., 23 Cl. Ct. 726, 733 (1991) (citing United States v. U.S. Gypsum Co., 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight")), aff'd, 968 F.2d 1226 (Fed. Cir. 1992).

However, there are situations in which compelling oral 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 & Human Servs., 69 Fed. Cl. 775, 779 (2006) ("like 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, 2005 WL 6117475, at *19 ("[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 & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley v. Sec'y of Health & Human Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

iii. Evaluation of Expert Testimony

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master may consider in evaluating the reliability of expert testimony and other scientific evidence. In Daubert v. Merrell Dow Pharm., Inc., the Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. 509 U.S. 579 (1993). In Terran v. Sec'y of Health & Human Servs., the Federal Circuit ruled that it is appropriate for special masters to utilize the Daubert factors as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases. 195 F.3d 1302, 1316 (Fed. Cir. 1999).

Daubert instructs fact-finders to consider "(1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." Terran, 195 F.3d at 1316 n.2 (citing Daubert, 509 U.S. at 592-95). In addition, where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness

of their competing theories." Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the ipse dixit of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (2009) (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)).

A treating physician's opinions are considered "quite probative," as treating physicians are in the "best position" to evaluate the vaccinee's condition. Capizzano, 440 F.3d at 1326. However, no treating physician's views bind the special master, per se; rather, their views should be carefully considered and evaluated. § 13(b)(1); Snyder, 88 Fed. Cl. at 745 n.67. Each opinion from a treating physician should be weighed against other, contrary evidence present in the record – including conflicting opinions from other treating physicians. Hibbard v. Sec'y of Health & Human Servs., 100 Fed. Cl. 742, 749 (Fed. Cl. 2011), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 136 (Fed. Cl. 2011), aff'd, 463 F. App'x 932 (Fed. Cir. 2012); Veryzer v. Sec'y of Health & Human Servs., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), aff'd, 100 Fed. Cl. 344 (2011).

iv. Consideration of Medical Literature

Both parties filed medical and scientific literature in this case, including some articles that do not weigh heavily on the outcome herein. The undersigned has reviewed and considered all of the medical literature submitted in this case, though the undersigned only discusses those articles that are most relevant to entitlement and/or are central to petitioner's case – just as the undersigned has not exhaustively discussed every individual medical record filed. Moriarty v. Sec'y of Health & Human Servs., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted)); see also Paterek v. Sec'y of Health & Human Servs., 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

B. Analysis

i. The Evidence Supports a POEMS Diagnosis with Onset in November 2013.

Although the parties agree that petitioner was appropriately diagnosed with POEMS syndrome, they firmly dispute the onset of the condition, as well as the appropriate diagnosis for her neuropathy-related symptoms in October and November 2013. Both sides devoted time at hearing to addressing whether vaccine-induced GBS could be shown to cause POEMS syndrome. The medical records in this case, however, suggest a more pertinent question: whether petitioner had GBS at all. The medical theory of causation proffered by petitioner hinges on the undersigned finding that her neuropathy-related symptoms in October and November 2013 are attributable to a GBS diagnosis, not POEMS. Therefore, if petitioner did not suffer from GBS at the outset, then her claim cannot succeed.

As Federal Circuit precedent establishes, in certain cases it is appropriate to determine the nature of a petitioner's injury before engaging in the Althen analysis. Broekelschen, 618 F.3d at 1346. Since "each prong of the Althen test is decided relative to the injury[,]" determining facts relating to the claimed injury can be significant in a case like this, where the petitioner has an evolving course of symptoms, resulting in a changed diagnosis. Id. Thus, before determining if petitioner has met each prong of Althen, the undersigned addresses whether she has established, by a preponderance of the evidence, that she suffered from GBS as a precursor illness to her later-diagnosed POEMS syndrome.

It is indisputable that petitioner's treaters considered both GBS and CIDP diagnoses over the course of her illness and followed the appropriate treatment protocol for both diseases. See, e.g., Pet. Ex. 7 at 54-55; Pet. Ex. 5 at 63-66, 681. The experts in this matter agreed that GBS and POEMS syndrome are distinct conditions, consistent with the descriptions outlined above. They differed, however, on the interpretation of petitioner's initial neuropathy-related symptoms in October 2013 as attributable to GBS or POEMS. Although there is earlier-in-time evidence in the medical records interpreting petitioner's course as GBS, and CIDP thereafter, those records by themselves, viewed in retrospect, suggest that petitioner more likely than not suffered from POEMS syndrome at the outset, rather than GBS or CIDP.

The medical records establish that petitioner began experiencing neuropathy-related symptoms in October and November 2013, initially thought to be indicative of GBS. See, e.g., Pet. Ex. 7 at 54-55; Pet. Ex. 5 at 681. Even after treatment in the months thereafter, however, petitioner experienced multiple relapses in her symptoms causing her treaters to suspect she may have CIDP. Her symptoms remained persistent through 2014, despite receiving treatment for presumed GBS and later CIDP, a fact Dr. Lipe noted and relied upon in opining that petitioner likely had POEMS syndrome from the early stages. Because GBS/CIDP and POEMS can be confused in their initial presentations, it is not surprising that the treating physicians who first saw petitioner in late 2013 reached different conclusions from those treating her later, in August 2014.

Laboratory testing, followed by an alteration of petitioner's treatment, also strongly supports the POEMS diagnosis. By August 2014, the fact that her symptoms, including neuropathy-related sequelae and thrombocytosis had still not fully cleared, and now included additional symptoms, such papilledema, prompted treaters to test petitioner for elevated serum VEGF based on her persistent neuropathic symptoms and positive SPEP testing. The medical literature strongly associates high-dose melphalan, cyclophosphamide, and stem cell transplantation with the successful treatment of POEMS. See, e.g., Pet. Ex. 29, Tab F at 219-20. Petitioner improved thereafter following similar treatment. Pet. Ex. 18 at 385-93; Pet. Ex. 19 at 27.

As noted earlier, petitioner objects to the POEMS diagnosis made in October/November 2013. Her experts seemingly posit that greater weight should be given to the views of her early-in-time treating physicians who made the initial GBS/CIDP diagnoses, despite the fact that petitioner's later-in-time treatment evaluations took into account her persistent and evolving symptoms. Indeed, petitioner's early treaters reached immediate conclusions about the nature of

petitioner's neuropathy-related symptoms without the benefit of the evidence Drs. Yee, Fogerty, and Dispenzieri later relied on, including the laboratory tests, altered treatment, and persistent/new onset of symptoms. There is no evidence in the record suggesting that any other treating physicians who saw petitioner *after* the POEMS diagnosis was established disagreed with the conclusions regarding her ultimate diagnosis, or posited that any precursor illness, like GBS, was appropriate.

The undersigned finds that Dr. Lipe's interpretation of the above-referenced records regarding disease onset and progression was ultimately more persuasive. Dr. Lipe based her opinion on a complete review of the record in light of petitioner's entire course. Having treated multiple POEMS patients, she observed that a patient may experience neuropathy-related symptoms long before they are actually diagnosed with POEMS and even before such a diagnosis might be proper based on the diagnostic criteria. Tr. 268-67. Because of the chronic nature of their symptoms, POEMS patients are routinely misdiagnosed with conditions similar to GBS, including AIDP and CIDP. Tr. 260-61, 282, 293.

Given the above, Dr. Lipe distinguished petitioner's initial neuropathy, including pain and edema, and persistent thrombocytosis as best attributable to POEMS in light of later records indicating the presence of monoclonal gammopathy, an increase in cherry angiomas, and elevated serum VEGF. Tr. 265-66, 284, 293. She posited that early examinations and test results did not display all of the formal criteria for the condition at onset which is typical based on the literature discussing its progression over time. See, e.g., Pet. Ex. 29, Tab Q; Resp. Ex. A, Tab 6.

Dr. Lipe was also more persuasive in identifying inconsistencies in petitioner's history that prolonged the initial POEMS syndrome diagnosis. Through her reading of petitioner's contemporaneous SPEP test results, she pointed out that early symptoms and testing actually supported a suspicion for a POEMS diagnosis prior to the date documented in the record—the beta spikes, for example, evident from petitioner's November 2013 SPEP test (see Pet. Ex. 5 at 770-71) were abnormal in her view. Tr. 268, 271. Dr. Lipe felt these spikes were likely concerning evidence of an underlying plasma cell disorder. Moreover, she explained that petitioner's initial treatment with IVIG therapy likely resulted in some positive improvement to her neuropathy-related symptoms in the early stages given it is the preferred treatment for the condition. Tr. 264, 295. All in all, however, petitioner's response to IVIG became less robust over time with no eventual resolution, as the medical record indicates. Dr. Lipe also pointed out that petitioner received steroid treatment during her multiple hospital stays, which could have resulted in additional improvement.

In response, petitioner's experts failed to establish a reasonable explanation for petitioner's course in light of her complete medical history. They placed too much emphasis on petitioner's earlier-in-time records and treatment responses, indicating that petitioner likely had GBS/CIDP. Indeed, petitioner's later-in-time treaters had the benefit of reviewing the additional evidence regarding petitioner's condition, for example, SPEP with immunofixation confirming the existence of monoclonal gammopathy and confirmed elevated serum VEGF levels. Drs. Latov and Parekh generally found more significant the initial GBS/CIDP diagnoses and the IVIG treatment she received thereafter without explaining the subsequent changes in her course and overall improvement following treatment for POEMS syndrome.

Furthermore, Drs. Latov and Parekh were selective in their interpretation of petitioner's multitude of symptoms without taking into consideration her POEMS course as a whole. For instance, Dr. Latov posited that petitioner's cherry angioma eruption and thrombocytosis were nonspecific findings in the context of both GBS and POEMS given their overall presence in the general population at large. Tr. 44-45. Dr. Parekh, by contrast, agreed that thrombocytosis could be attributable to POEMS syndrome, but he maintained it was not enough to diagnosis the condition. Tr. 245-46. In so stating, both experts interpreted the above-described symptoms in isolation of petitioner's entire course, without taking into consideration the progression of her symptoms and relevant laboratory testing in retrospect.

Regarding petitioner's cranial nerve symptoms, Drs. Latov and Parekh maintained that instances of drooling are best attributable to a GBS diagnosis. Tr. 24, 55, 76, 231. POEMS, by contrast, is typically not associated with cranial nerve involvement. See Resp. Ex. A, Tab 6 at 678 (case report of POEMS patient indicating "no cranial and autonomic nerve involvement" upon exam). Upon further questioning, however, Dr. Latov acknowledged that there are instances of POEMS-related cranial nerve dysfunction reported in the older literature. Tr. 59. Dr. Lipe agreed that drooling is not a typical POEMS-related symptom, but she maintained that pulmonary and swallowing difficulties are attributable to POEMS syndrome. Tr. 267; see Resp. Ex. C, Tab 3 at 2500-01; Pet. Ex. 31, Tab C at 955. Along those same lines, Dr. Bourdette maintained that R.S.'s drooling was likely a consequence of the respiratory and swallowing problems she experienced, which would be attributable to the lower cranial nerve. Tr. 98-100; see Resp. Ex. H at 971.

All in all, Dr. Lipe was more persuasive in discussing what was relevant in diagnosing POEMS based on evidence from contemporaneous medical records before and after petitioner's actual date of diagnosis and the relevant medical literature. In so doing, she convincingly offered an interpretation of the medical history that petitioner has not rebutted. It is thus improbable that petitioner suffered from distinct GBS as a precursor illness to her later-diagnosed POEMS syndrome.

ii. Althen Analysis

1. Althen Prong One: Petitioner's Medical Theory

Under Althen Prong One, petitioner must set forth a medical theory explaining how his flu vaccine could have caused the injury alleged. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioner relies upon a medical opinion to support his theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d at 1347 ("[t]he 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 & Human 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's conclusion that petitioner likely did not suffer from GBS at the outset of her illness largely moots petitioner's arguments that the flu vaccine played any role in her development of POEMS syndrome thereafter, given that petitioner's theory requires a finding that she experienced vaccine-induced GBS. The undersigned will, however, consider the evidence offered by petitioner in support of the first Althen prong under the assumption that petitioner offered preponderant evidence in support of a GBS diagnosis.

The molecular mimicry theory has been accepted in the Vaccine Program as a reliable explanation for how the flu vaccine can initiate an autoimmune process resulting in GBS. See, e.g., Reichert v. Sec'y of Health & Human Servs., No. 16-697V, 2018 WL 4496561, at *15 (Fed. Cl. Spec. Mstr. Aug. 2, 2018). Indeed, both Drs. Latov and Parekh offered reputable scientific literature associating the flu vaccine with an onset of GBS thereafter via the mechanistic process of molecular mimicry. See, e.g., Pet. Ex. 29, Tab P at 105.

Apart from her inability to show that she more likely than not suffered from GBS at the outset, however, petitioner has also failed to preponderantly establish that chronic inflammation produced secondarily due to GBS can result in plasma cell proliferation let alone instigate POEMS syndrome specifically. As discussed above, Drs. Latov and Parekh propose that the chronic stimulation of B-cells can cause the body to produce an abundance of plasma cells. Tr. 33, 50-51, 232, 240-41. The medical articles offered in support, however, do not support this assertion. Notably, none of the articles cited by petitioner's experts associate chronic immune stimulation pathologically with the onset of POEMS syndrome. See, e.g., Pet. Ex. 29, Tab E; Pet. Ex. 31, Tab M; Pet. Ex. 31, Tab W; Pet. Ex. 61. Indeed, the mouse model evidence offered by Dr. Parekh shows only that the mineral oil, pristane, a substance wholly distinguishable from a vaccine, can stimulate plasma cell growth. See, e.g., Pet. Ex. 68; Pet. Ex. 60.

At best, petitioner offered the Lindqvist article to establish that patients with an established autoimmune disease have an increased risk of developing a plasma cell disorder. See Pet. Ex. 59 at 6284. As the undersigned discussed at length above, however, petitioner has not preponderantly established that she suffered from an autoimmune condition, whether GBS or CIDP, as a result of the flu vaccine. Moreover, the relevant literature offered by experts on both sides which discusses the pathogenesis of POEMS syndrome makes no mention of immune stimulation, whether chronic or acute, as an acceptable biologic mechanism capable of causing the condition. Petitioner's expert, Dr. Latov, even acknowledged at hearing that petitioner's case would be the first reported instance of POEMS syndrome occurring as a direct result of GBS/CIDP via the mechanism posited herein. Tr. 54. Such a novel theory, without more persuasive scientific evidence, does not rise to the level of sound and reliable. See Boatman, 941 F.3d at 1360.

Another questionable element of petitioner's theory is her proposition that cytokine upregulation, presumably attributable to the flu vaccine, could have played a pathogenic role in the development of POEMS syndrome. Petitioner's experts have referenced medical literature showing that mice injected with various cytokine variants can express an over production of

plasma cells. Moreover, there is some evidence in the record suggesting that elevated serum VEGF levels are thought to be associated with POEMS syndrome pathogenesis. See, e.g., Pet. Ex. 29, Tab F at 215. Drs. Latov and Parekh have further discussed literature showing that VEGF has been shown to be elevated in the POEMS population at large. Even so, petitioner has not persuasively shown how a vaccine or its components can stimulate VEGF or any other cytokine, so as to cause POEMS syndrome.

In summary, petitioner has not offered a sound and reliable medical theory in support of her claim. Petitioner has not met the preponderant evidentiary standard with respect to the first Althen prong.

2. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, a 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).

As noted above, the medical record and testimony herein establishes that petitioner suffers from POEMS syndrome, with the first symptom manifesting in October and November 2013. The undersigned's findings with respect to the medical theory proffered in this case along with the appropriate diagnosis for petitioner's symptoms make it impossible for the undersigned to conclude that petitioner successfully established a logical cause-and-effect sequence that in this case the flu vaccine "did cause" petitioner's POEMS syndrome or that the vaccine initiated GBS, which caused POEMS. Without being able to establish a reliable medical theory, or that she suffered from GBS, petitioner cannot show that the vaccine more likely than not caused her illness thereafter.

Although some of petitioner's treaters made some reference to her onset of symptoms being temporally related to the flu vaccine, they did so based on the assumption that she had experienced GBS or CIDP at the outset. Following her diagnosis with POEMS, no treaters appear to have embraced an association between the flu vaccine and petitioner's subsequent development of POEMS. Indeed, even petitioner's experts acknowledged that vaccines likely do not play a causative role in the development of POEMS syndrome.

3. Althen Prong Three: Proximate Temporal Relationship

Under Althen Prong Three, petitioner must provide "preponderant proof that the onset of symptoms occurred within a time[] frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The acceptable temporal association will vary according to the medical theory advanced in the case. See Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356

(explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting [the] vaccine and injury").

Roughly two weeks passed between petitioner's receipt of the flu vaccine and the onset of her symptoms initially thought to be caused by GBS. There is support in the relevant medical literature for the conclusion that the timeframe between vaccination and petitioner's subsequent symptoms was medically acceptable—assuming she suffered from GBS as she alleges. See, e.g., Pet. Ex. 29, Tab P at 105.

However, as outlined above, petitioner has not established that she more likely than not suffered from GBS at the outset of her illness. Moreover, even if petitioner had accepted the conclusion that her symptoms in October and November 2013 were indicative of POEMS, and argued that it was caused by her receipt of the flu vaccine, there would still be a lack of a medically-acceptable temporal relationship, due to the fact that neither Dr. Latov nor Dr. Parekh proposed that vaccinations could cause POEMS syndrome at all let alone offered some medically cognizable timeframe for such an injury. Petitioner thus has not met her burden on the third Althen prong.

VII. CONCLUSION

POEMS syndrome has caused significant distress in petitioner's life, and the undersigned empathizes with her dedicated search for medical and scientific answers. However, for all the reasons discussed above, the undersigned finds that petitioner has not established by preponderant evidence that she is entitled to compensation and her petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master