In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-731V
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PUBLISHED

C.F., Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner Human papillomavirus ("HPV") vaccine; Postural orthostatic tachycardia syndrome ("POTS")

Robert J. Krakow, Law Office of Robert J. Krakow, P.C., New York, NY, for petitioner.
Zoe Wade, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On July 15, 2015, petitioner[2] filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[3] alleging that she suffered postural orthostatic tachycardia syndrome ("POTS") caused by a human papillomavirus ("HPV") vaccine administered on July 19, 2012. (ECF No. 1, p. 2.) For the reasons set forth below, I conclude that petitioner is not entitled to compensation.

[1] When this decision was originally filed the undersigned advised his 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 redactions, namely reduction of petitioner's name to initials. 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] In fact, the petition was initially filed by Ms. F.'s parents while she was still a minor. The caption was changed on July 2, 2018, when she reached the age of majority. (ECF No. 71.) This decision will refer to "petitioner" in her singular capacity even when referring to periods during which her parents were the named petitioners.

[3] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34,

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make several factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally—and the key question in most cases under the Program—the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable timeframe following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). Because POTS is not listed as an injury on the Vaccine Injury Table, petitioner must satisfy this burden of proof.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based

solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, [petitioner's] burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If [petitioner] satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be based upon "sound and reliable" scientific explanation. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The *Althen* court also indicated that, in finding causation, a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280.

II. Procedural History

The petition for compensation and accompanying medical records were filed on July 15, 2015. (ECF Nos. 1, 6-8.) On August 3, 2015, this case was reassigned to Special Master Millman. (ECF No. 11.) Petitioner continued to file updated medical records between September 24, 2015 and November 22, 2016. (ECF Nos. 13-18, 22, 26, 35-38.) Petitioner filed a declaration documenting the progression of her condition on January 9, 2017. (ECF No. 40.) After filing her medical records, petitioner filed an expert report by autonomic specialist Svetlana Blitshteyn, M.D. (ECF Nos. 46-50.)

Respondent filed his Rule 4(c) report recommending against compensation accompanied by an expert report from autonomic specialist Christopher H. Gibbons, M.D., on July 28, 2017. (ECF Nos. 53, 54.) Petitioner filed a responsive expert report by Dr. Blitshteyn on October 10, 2017. (ECF Nos. 58, 59.) Respondent then filed a supplemental report by Dr. Gibbons on December 19, 2017. (ECF No. 66.) Following the parties' exchange of expert reports, petitioner filed additional medical records on February 5, 2018, and July 23, 2018. (ECF Nos. 68, 72.)

This case was reassigned to my docket on June 5, 2019. (ECF No. 74.) On July 12, 2019, the parties filed a joint status report confirming that this case was ripe for a hearing. (ECF No. 76, pp. 1-2.) I subsequently scheduled a two-day entitlement hearing to commence on June 9, 2020. (ECF No. 82.) Due to the coronavirus pandemic, the parties later agreed to reschedule the entitlement hearing to commence on June 9, 2021. (ECF Nos. 87-89.) In preparation for the hearing, the parties filed additional medical literature in March and April 2021. (ECF Nos. 90, 95.) Subsequently, the parties filed prehearing briefs on May 19, 2021. (ECF Nos. 104, 107, 109.)

A virtual entitlement hearing was held on June 9 and 10, 2021. (*See* ECF Nos. 114-15, Transcript of Proceedings ("Tr.").) Petitioner, Dr. Blitshteyn, and Dr. Gibbons testified. Following the entitlement hearing, petitioner a filed post-hearing brief on October 25, 2021. (ECF No. 118.) Respondent then filed a responsive post-hearing brief on February 11, 2022, followed by petitioner's reply brief on March 14, 2022. (ECF Nos. 124, 126.) This case is now ripe for a ruling on entitlement.

III. Factual History

a. As Reflected in Medical Records

Prior to her HPV vaccination on July 19, 2012, petitioner was relatively healthy. Petitioner experienced some mild illnesses during her infancy, including fevers, ear infections, and congestion. (Ex. 21, pp. 35, 37, 40, 47; Ex. 32, pp. 96, 99, 102, 110.) As a pre-teen, she suffered several minor injuries to her left foot, left wrist, left hand, and right ankle. (Ex. 21, pp. 15, 20, 24, 60-61; Ex. 32, pp. 52, 64, 83, 127.) Petitioner also underwent a tonsillectomy and adenoidectomy prior to receiving her HPV vaccination. (Ex. 25, pp. 11-12.) The medical records document a history of headaches beginning around the time she entered kindergarten. (*See*, *e.g.*, Ex. 21, p. 26, 32.)

Petitioner received her third dose of the Gardasil HPV vaccine on July 19, 2012. (Ex. 1, p. 5.) She had previously received her first two doses during the prior year on July 22, 2011, and November 19, 2011. (*Id*.) On the date of her third vaccination, petitioner complained of a "frontal" headache persisting for one week. (Ex. 10, p. 28.)

Roughly three months later, petitioner saw Dr. Matthew C. Weiland at the HealthWest Physicians Clinic on October 9, 2012. (Ex. 10, p. 26.) Petitioner reported that she had been experiencing daily headaches since July, typically beginning in the morning and lasting for about thirty minutes. (*Id.*) She also reported experiencing more stress recently due to school. (*Id.*) Petitioner denied any other neurological symptoms such as vision changes, difficulty walking, or pre-headache auras. (*Id.*) Dr. Weiland prescribed Mobic, a nonsteroidal anti-inflammatory, for petitioner's headaches and recommended she see a pediatric neurologist. (*Id.* at 27.)

Petitioner returned to Dr. Weiland on March 22, 2013, with a primary complaint of headaches that had become more constant and painful. (Ex. 10, p. 19.) She reported that her headaches were mainly in her forehead and back of her neck and had been impacting her sleep. (*Id.*) Dr. Weiland noted that petitioner responded well to Mobic "through the month of January" and had delayed her neurology consult to April "because she was doing so well." (*Id.*) Dr. Weiland ordered CBC, CMP, and TSH labs, increased petitioner's Mobic dosage, prescribed Flexeril, and scheduled a neurology consult. (*Id.* at 20.)

Petitioner visited neurologist Dr. James E. Nelson on April 10, 2013. (Ex. 31, p. 124.) Dr. Nelson noted that petitioner's headaches began in July 2012 with no clear trigger. (*Id.* at 125.) Petitioner reported that prior to her headaches, she had hand-to-head contact with her sister but did not lose consciousness, fall, or experience any swelling. (*Id.*) She stated that Mobic provided temporary relief but that her headaches had returned. (*Id.*) She also reported that she was now experiencing photo/phonophobia during her headaches. (*Id.*) Dr. Nelson assessed petitioner as suffering from "chronic daily headache with migraine features" and prescribed amitriptyline.[4] (*Id.* at 126-27.)

On April 30, 2013, petitioner went to the emergency department at the Children's Hospital & Medical Center where she was admitted for persistent headaches. (*See* Ex. 33, p. 34; Ex. 31, p. 75.) The hospital admission summary noted that petitioner's headaches began in July 2012, had increased in frequency, and had become daily in the last three months. (Ex. 31, p. 75.) Petitioner reported that some headaches would persist for twenty-four hours and that she had missed school and stopped playing soccer as a result. (*Id.*)

During her hospitalization, Dr. Nelson assessed petitioner with a history of "medication overuse", chronic daily headache, and migraine (without aura) signs. He believed that petitioner was "still inside the window to get a rebound headache from medication overuse," but needed to rule out any secondary causes. (Ex. 31, p. 81.) Dr. Nelson discontinued amitriptyline, prescribed Depakote for petitioner's migraine, IV steroids, and ordered an MRI. (*Id.*) Petitioner underwent a brain MRI with and without contrast on April 30, 2013. (Ex. 33, p. 24.) The MRI revealed "patchy foci of subcortical increased T2/FLAIR signal . . . primarily involving the bilateral superior frontal lobes." (*Id.*) The results were interpreted as nonspecific and potentially representative of "gliosis/encephalomalacia, demyelinating process (including ADEM), inflammation/infection, or less likely, metabolic process."[5] (*Id.* at 25.) Petitioner's bloodwork from May 1, 2013, showed elevated CO2, chloride, and glucose levels. (Ex. 31, p. 76.) Petitioner was mildly tachycardic leading doctors to order additional testing, including an EKG, bloodwork, and urinalysis. (*Id.*) Petitioner's EKG showed sinus

[4] Dr. Nelson noted side effects of amitriptyline include "sedation, nausea, constipation, [and] rare heart issues." (Ex. 31, p. 127.)

[5] The MRI was later interpreted by Dr. John Bodensteiner at the Mayo Clinic. (Ex. 22, p. 4.) Dr. Bodensteiner concluded that petitioner's MRI findings of hyperintensity in the frontal lobe representing perivascular spaces was commonly seen in patients with migraine. (*Id.*)

tachycardia with a rate of 122 beats per minute ("bpm"). (*Id.*) Petitioner was discharged from the Children's Hospital on May 2, 2013. (*Id.* at 75.)

After her discharge from the hospital, petitioner followed up with Dr. Weiland on May 6, 2013. (Ex. 10, p. 13.) She reported that her new medications were not improving her symptoms, her headaches had remained painful, she had fever and nausea, and she was experiencing occasional heart racing and fatigue. (*Id.*) Dr. Weiland diagnosed petitioner with chronic daily headaches and tachycardia. (*Id.* at 14.) He scheduled petitioner for a Holter monitor to measure her heartrate and prescribed propranolol for her headaches. (*Id.*) Petitioner's Holter monitor showed a heart rate range of 54-183 bpm with an average heart rate of 103 bpm. (Ex. 3, p. 29.)

Petitioner followed up with Dr. Nelson on May 14, 2013. She reported new symptoms of tingling in her arms and legs as well as chest and shoulder pain. (Ex. 31, pp. 128-29.) Dr. Nelson explained that petitioner presented a "complex medical situation," and that treating physicians had yet to diagnose a "specific underlying cause." (*Id.* at 131.) He continued treating petitioner for "migraine/pain syndrome" and referred her to headache specialist Dr. Chad Whyte. (*Id.*)

Petitioner saw pediatric cardiologist Dr. John D. Kugler on May 15, 2013. (Ex. 31, p. 120.) Dr. Kugler noted that since petitioner's elevated heart rate was detected, she had noticed her heart beating faster. (*Id.*) Petitioner reported that her headaches were occurring daily but had started less frequently in July 2012. (*Id.*) Dr. Kugler reviewed petitioner's EKG from the hospital and her Holter monitor results and found no evidence of a primary cardiac problem. (*Id.*) Dr. Kugler's cardiac monitoring on several dates in May 2013 reflected sinus tachycardia. (Ex. 3, p. 16.) Her results from May 22, 2013, showed a heart rate range of 97 bpm to 139 bpm, with heart rate elevations associated with symptoms of chest pain and headache. (*Id.*) Dr. Kugler concluded that petitioner's tachycardia was "highly likely related to a secondary problem" such as her headaches or an anxiety disorder. (Ex. 31, p. 122.)

On May 29, 2013, petitioner saw pediatric psychologist Keith Allen, Ph.D. (Ex. 2, p. 1.) She reported experiencing chronic and progressively worsening headaches since July 2012, but could not detect a pattern for her headaches. (*Id.* at 3.) She noted that school-related stress, fatigue, and physical exertion appeared to trigger or exacerbate her headaches. (*Id.*) Dr. Allen recommended that petitioner participate in pain management classes to better cope with her headaches. (*Id.* at 3-4.) At a follow-up visit on June 11, 2013, Dr. Allen focused on pain management, sleep hygiene, diet management, relaxation skills, cognitive coping, trigger management, and problem solving. (*Id.* at 5.) Petitioner continued to see Dr. Allen through August 14, 2013, focusing on the same pain management plan proposed at her June 11 visit. (*See* Ex. 2, pp. 5-9.)

Petitioner saw Dr. Weiland again on June 24, 2013, for complaints of chest pain and difficulty breathing in addition to continuing headaches. (Ex. 10, p. 8.) Petitioner explained that her chest pain "comes and goes for a few hours a day." (*Id.*) Dr.

Weiland noted that petitioner's prescription for Depakote was recently doubled. (*Id.* at 9.) Dr. Weiland diagnosed petitioner's chest pain as costochondritis and prescribed prednisone. (*Id.*) He also referred petitioner to a new neurologist as Dr. Nelson had moved. (*Id.*)

On July 3, 2013, petitioner visited neurologist Dr. Robert Sundrell. (Ex. 31, p. 132.) Petitioner reported previously using Mobic and Flexeril, which provided temporary relief, followed by Topamax and amitriptyline, which caused side effects, then Depakote. (*Id.*) Petitioner was still on Depakote at the time of the visit but was worried it was causing her recent chest pain. (*Id.*) Dr. Sundrell's neurological assessment was normal. (*Id.* at 133.)

Petitioner next saw allergist Dr. Bob K. Miyake on July 15, 2013, to undergo testing to determine the cause of her headaches. (Ex. 26, p. 10.) Dr. Miyake performed an aeroallergen skin test as well as tests for corn, milk, and wheat allergies, all of which were negative. (*Id.*) Dr. Miyake suspected that it was unlikely that petitioner's headaches were caused by an IgE-mediated mechanism and believed the more likely culprit to be "some type of primary headache disorder whether . . . migraine or some other variant." (*Id.* at 11.) He believed that petitioner's occasional rhinorrhea was related to her underlying headache disorder and suggested two over the counter nasal sprays as needed. (*Id.*)

Petitioner saw neurologist and headache specialist Dr. Chad Whyte on July 26, 2013. (Ex. 31, p. 134.) Dr. Whyte noted that petitioner reported getting headaches since the age of seven, and that they had increased in frequency over the years. (*Id.*) Petitioner's review of symptoms reflected fatigue, neck pain, chest pain, myalgias, dizziness, headaches, sleep disturbance, and anxiety. (*Id.* at 135.) A physical examination revealed mild tenderness to palpation of the right-sided cervical paraspinous muscles. (*Id.* at 136.) Dr. Whyte diagnosed petitioner with chronic migraine, migraine without aura, cervicalgia, sleep disturbance NOS, and abnormal brain MRI. (*Id.*) Dr. Whyte switched petitioner to Depakote ER and Zomig to manage her migraines and considered trazodone or a polysomnogram if her sleep disturbances persisted. (*Id.*) Dr. Whyte also recommended a follow-up brain MRI. (*Id.*)

On August 5, 2013, petitioner followed up with Dr. Whyte. She reported that during a vacation she developed a low-grade fever, body pain, and an increase in her headache pain. She then developed swollen joints and erythema after taking a Medrol Pak. (ECF No. 7-9, p. 11.) Dr. Whyte diagnosed petitioner with chronic migraine, migraine without aura, and fibromyalgia. (*Id.* at 12.) He was unsure why petitioner responded so poorly to the previous medication and ordered bloodwork to measure petitioner's ANA level. (*Id.*) He prescribed Depakote ER with Cymbalta, tizanidine, and Naproxen. (*Id.*) Dr. Whyte also considered an infusion for later that week if petitioner's symptoms persisted. (*Id.*)

On September 1, 2013, petitioner reported to the emergency department at the Children's Hospital with a chief complaint of headache, chest pain, and cough. (Ex. 33,

p. 89.) She reported that her current headache had lasted four days. (*Id.*) She denied vomiting, dizziness, or change in consciousness or orientation but noted that she was experiencing chest pain and light sensitivity. (*Id.* at 89-90.) Petitioner was given a "migraine headache cocktail of 1l NS, reglan, Benadryl, Toradol, Zofran, and decadron," which alleviated her pain and allowed her to be discharged the same day. (*Id.*)

Petitioner returned to Dr. Whyte on September 5, 2013. (Ex. 31, p. 145.) Dr. Whyte noted that petitioner had tried various medicines without success due to her "reactions to them." (*Id.* at 146.) He noted however, that petitioner experienced these same reactions without medication. (*Id.*) Although petitioner denied anxiety and stress, Dr. Whyte seemed to believe that petitioner's "flat affect and lack of eye contact with [him]" suggested otherwise. (*Id.*) Dr. Whyte noted that petitioner no longer experienced tenderness to palpation associated with fibromyalgia and diagnosed petitioner with chronic intractable migraine, migraine without aura, sleep disturbance, and unclear somatoform complaints. (*Id.*) Dr. Whyte wondered if there was "significant undetected depression and/or anxiety," that would explain petitioner's symptoms. (*Id.* at 147.) He planned to get petitioner approved for Botox as a last resort, administered Migranal at the visit, and provided Benadryl and Phenergan injections for home emergency use. (*Id.*)

Petitioner began treatment with chiropractic neurologist Dr. Ronald R. Evans on September 7, 2013. (Ex. 28, p. 8.) At her first visit, petitioner underwent a paraspinal surface electromyographic scan ("sEMG"). (*Id.*) Dr. Evans found that petitioner showed "phase 1 degeneration" and loss of normal cervical spine lateral curve. (*Id.*) He recommended a course of chiropractic adjustments, electric muscle stimulation, and intersegmental traction. (*Id.* at 8.) Petitioner saw Dr. Evans for chiropractic treatment roughly three times per week between September 7, 2013, and February 18, 2014, with little to no improvement in her headache symptoms. (*See* Ex. 28, pp. 8-44.) Following her initial course of treatment, petitioner returned periodically to Dr. Evans for similar treatment between March 25, 2014, and September 10, 2015. (*See id.* at 45-55.)

Petitioner had a follow-up visit with Dr. Whyte on January 20, 2014. (Ex. 31, p. 185.) She reported that her early chiropractic treatment was providing some relief. (*Id.*) Dr. Whyte chose not to prescribe Botox at this point and instead prescribed a low dose of sertraline. (*Id.*)

On February 19, 2014, petitioner saw family medicine doctor Jeffrey L. Gartrell with a chief complaint of headaches and chest pain. (Ex. 32, p. 29.) Petitioner described her chest pain as starting on the left chest wall and radiating into her left arm. (*Id.*) Dr. Gartrell diagnosed petitioner with chronic migraines and chest pain of unknown etiology. (*Id.* at 30.)

Petitioner saw allergist Dr. William Ingram from March 19, 2014, to April 16, 2014, to evaluate for various allergies. (*See* Ex. 36.) Following petitioner's testing, Dr. Ingram concluded that petitioner was "allergic to TCE dose per profocol . . . allergic to

molds, trees . . . allergic to cat, dog, cockroach, trees, grasses, weeds, smuts, [and] corn pollen." (Ex. 36, pp. 9-12.)

On April 8, 2014, petitioner saw pediatric rheumatologist Dr. Emilina M. Lim for an autoimmune evaluation. (Ex. 31, p. 157.) Petitioner reported "episodic color changes" in her knees, diffuse arthralgias without stiffness or swelling, and myalgias. (*Id.*) Dr. Lim observed that petitioner's symptoms appeared to worsen over the past year and occurred randomly without a known trigger. (*Id.*) Dr. Lim observed hypermobile joints but an otherwise unremarkable exam. (*Id.* at 161.) Dr. Lim believed petitioner's musculoskeletal complaints were primarily driven by her hypermobile joints, but conceded that the intermittent and random nature of petitioner's condition made a defining diagnosis less clear. (*Id.*) She observed that petitioner had an elevated ESR with an unclear etiology and recommended a repeat test three to four weeks later. (*Id.*) Dr. Lim proposed possible amplified musculoskeletal pain syndrome ("AMPS") but did not record any diagnoses. (Ex. 31, p. 161.) Dr. Lim discussed strategies for chronic pain management and suggested physical therapy and orthotics. (*Id.*)

Petitioner saw Dr. Whyte on April 22, 2014, for a follow-up visit. (ECF No. 7-9, p. 7.) Petitioner reported that her headaches had been less frequent, but still occurred more than half of the time during the month. (*Id.*) Petitioner reported that none of her headaches had been severe, and that her rheumatologist believed she suffered from fibromyalgia. (*Id.*) Petitioner also reported one week of hip pain, lower body joint pain, and pruritic rash. (*Id.*) Dr. Whyte added "possible fibromyalgia" and "anxiety" to petitioner's list of diagnoses. (*Id.* at 8.) He put petitioner back on Depakote, added Savella for her other symptoms, trazodone for sleep, and referred her to her primary care physician to address her rash. (ECF No. 7-9, p. 8.) Dr. Whyte noted that there are instances of rash with fibromyalgia, but there was no obvious phenotype of the disease. (*Id.*)

Petitioner received a cervical spine MRI without contrast on May 19, 2014, which revealed no abnormalities. (ECF No. 7-9, p. 15.)

On June 17, 2014, petitioner again returned to Dr. Whyte for a follow-up appointment. (ECF No. 7-9, p. 5.) Petitioner reported that she had been doing well since her last visit, but that she recently developed increased heart rate, vision loss, and poor sleep. (*Id.*) Dr. Whyte noted that petitioner was more tender to palpation on this visit, and therefore her fibromyalgia was more evident. (*Id.* at 6.) Dr. Whyte started petitioner on lipoic acid for her lightheadedness. (*Id.*) Petitioner's next visit to Dr. Whyte was on September 16, 2014. (*Id.* at 4.) Petitioner reported that she had done well over the summer "with little, if any headaches." (*Id.*) However, petitioner's headaches had started up again during the previous few weeks, and she had seen an allergist who believed that she was having a reaction to corn which could have contributed to her headaches. (*Id.*) Petitioner returned to Dr. Whyte three months later for a follow up on December 17, 2014. (*Id.* at 2.) She reported that she experienced migraines one to two times per week and near daily headaches. She was taking indomethacin five days per week and was now experiencing "painful, red, swollen lower

extremity joints lasting 45-90 minutes at a time," however "the rheumatologist [did] not think this is a rheumatologic disorder." (*Id.*) Dr. Whyte noted that he was "not sure what to make of [petitioner's] symptoms. She does not respond to typical medicines and did well during the summer. But now she has a lot of body aches and headaches." He concluded that petitioner needed a more thorough rheumatologic evaluation. (*Id.* at 3.)

On January 28, 2015, petitioner was admitted to the Children's Hospital ED with a chief complaint of headache. (Ex. 33, p. 164.) Petitioner reported suffering from a migraine lasting three and a half weeks with symptoms of photophobia and phonophobia. (*Id.*) She had tried abortive medication twice, but it was ineffective. (*Id.*) The ED doctors assessed petitioner with migraine and discussed migraine management and supportive care with her, but otherwise offered no specialized treatment. (*Id.* at 163.) Petitioner was discharged several hours later on January 29, 2015. (*Id.* at 164.)

Petitioner next reported to Dr. Virginia M. Ripley on February 5, 2015, with complaints of body aches, fever, nausea, weakness, sore throat, and coughing. (Ex. 10, p. 3.) Dr. Ripley suspected a viral etiology and ordered CBC, monospot, and flu testing, all of which were negative. (*Id.* at 4-5.) Dr. Ripley suggested that petitioner's suspected viral infection would resolve by the weekend, and discharged petitioner the same day. (Ex. 31, p. 49.)

Petitioner returned to Dr. Whyte on March 23, 2015. (ECF No. 7-9, p. 1.) She explained that she had "[done] well in February after trying to come off Depakote without success." (*Id.*) This is the first time that petitioner questioned whether her pain symptoms were related to her Gardasil vaccination. (*Id.*) Petitioner also reported lightheadedness and explained that her abortive medications were not effective. (*Id.*) Dr. Whyte noted that he was unfamiliar "with vaccines causing symptoms similar to a post-viral syndrome" but decided to "leave this for Dr. Biskup to figure out." (*Id.* at 2.) He prescribed verapamil as a preventative, alpha lipoic acid for dizziness, and Benadryl injections as an abortive. (*Id.*)

On March 27, 2015, petitioner was admitted to the Children's Hospital ED with a complaint of a week-long headache and intermittent knee and ankle pains. (ECF No. 6-3, p. 56.) Petitioner again reported that she believed her headaches may be related to her HPV immunization. (*Id.*) Attending physicians provided IV NS bolus, Toradol, Benadryl, and Compazine, which significantly improved petitioner's headache, while a 2 mg dose of IV valium provided relief for petitioner's joint aches. (*Id.* at 58.) Petitioner was discharged later that day. (*Id.*)

Petitioner saw Dr. Ripley again on April 22, 2015, with complaints of abdominal pain. (Ex. 31, p. 34.) Petitioner reported that she had been seeing Dr. Ingram who had administered IV vitamin C infusions. (*Id.*) Petitioner reported nausea both times after the infusions. (*Id.*) Petitioner's mother reported that petitioner's vision "goes black when she stands up . . . . her feet turn red sometimes . . . . [and] that [petitioner] has chest pain, migraines, and joint pain." (*Id.*) Dr. Ripley suspected that petitioner's abdominal pain was caused by an ovarian cyst and ordered urinalysis and a pelvic

ultrasound. (*Id.* at 36.) Petitioner's urinalysis and ultrasound were both normal, and Dr. Ripley advised that petitioner stop the vitamin C infusions with Dr. Ingram. (*Id.* at 37.)

Petitioner saw gynecologist Dr. Amber R. Cohn on April 23, 2015, for her lower pelvic and abdominal pain. (Ex. 35, p. 25.) Based on petitioner's normal ultrasound, Dr. Cohn did not believe that petitioner's pain was consistent with a gynecologic etiology, referred petitioner to a gastrointestinal specialist, and ordered additional bloodwork and an ultrasound to evaluate petitioner's liver and gallbladder. (*Id.* at 27.)

On April 27, 2015, petitioner returned to Dr. Kugler for her chest pain and vision changes with lightheadedness. (Ex. 19, p. 10.) Petitioner described her pain as a "stabbing feeling mid sternal, [lasting] a few minutes to all day and can come on at any time including with inactivity. It is exacerbated by taking deep breaths." (*Id.*) She also explained that her vision changes occurred upon standing up and lasted "a few seconds." (*Id.*) Petitioner's parents reported to Dr. Kugler that they believed petitioner's condition may be POTS and asked if it could be a post-vaccination syndrome. (*Id.*) Petitioner's parents also reported that petitioner continued to suffer from "sudden knee pain during which she will have red knees lasting 10-15 minutes and will be completely random." (*Id.* at 11.) Dr. Kugler found no evidence of a cardiac etiology for petitioner's chest pain but believed that it was "very consistent" with an idiopathic or chest wall pain. (*Id.*) He did, however, believe that petitioner's dizziness upon standing up was "very consistent with a postural orthostatic neurocardiogenic / neurocardioinhibitory / vasovagal mechanism." (Ex. 19, p. 11.) He also believed that petitioner's elevated heartrate symptoms were consistent with sinus tachycardia, but that her additional pain symptoms and skin rash were unrelated to a cardiac etiology. (*Id.* at 11-12.)

Petitioner followed up with Dr. Whyte again on June 23, 2015. (Ex. 31, p. 32.) Petitioner reported that she was experiencing daily headaches again over the previous four months and had 2 visual auras in addition to twice-a-week migraines. (*Id.*) Dr. Whyte reported that petitioner was to be seen at Mayo Clinic for a dysautonomia evaluation. (*Id.*) Dr. Whyte again proposed Botox for petitioner's migraines, and "CoQ10 for aura protection." (*Id.* at 33.)

Petitioner began seeing pediatrician Dr. Philip R. Fischer at the Mayo Clinic on July 2, 2015, for her migraines, tachycardia, vision changes, and joint pain. (Ex. 22, p. 5.) Dr. Fischer noted that petitioner's consistent headaches began "[c]oincidentally…a week or two after she had routine vaccines" and that "there was no other known trigger of illness or injury." (*Id.*) Petitioner also reported that for the last six months to a year, she started to get dizzy and lose her vision upon standing. (*Id.*) She further reported taking Savella for the past year and taking trazadone until two months prior. (*Id.* at 39.) Dr. Fischer conducted a stand test and documented petitioner's heart rate to be 90 bpm resting supine and 130 bpm standing. (Ex. 34, p. 40.) Dr. Fischer preliminarily diagnosed petitioner with chronic pain and chronic fatigue but suspected that petitioner had POTS. (*Id.*) Dr. Fischer ordered exercise testing to gauge petitioner's deconditioning given the possibility that "some of her changes [could be] related to debilitation from the chronic pain." (*Id.*)

While at the Mayo Clinic, petitioner underwent autonomic testing, including a tilt table test, a QSWEAT test, and a Valsalva maneuver test. (Ex. 34, pp. 53-55.) Petitioner's heart rate and blood pressure responses to the Valsalva maneuver were normal. (*Id.* at 53.) Her QSWEAT results were "normal for all sites." (*Id.*) While no orthostatic hypotension was observed during the tilt table test, petitioner's heart rate rose 38 bpm, from 111 bpm while supine to 149 bpm after being tilted up at 70 degrees for ten minutes. (*Id.* at 54.)

Upon reviewing petitioner's autonomic test results, Dr. Fischer sent an email to petitioner noting that "[petitioner's] heart was going fast at 'rest,' and it sped up LOTS more during the tilting. It looks like [petitioner does] have POTS." (Ex. 34, p. 36.) Additionally, Dr. Phillip Low, an autonomic expert at the Mayo Clinic, reviewed petitioner's autonomic testing. Dr. Low concluded: "Abnormal study. There is no evidence of autonomic failure on this study. There is resting and symptomatic orthostatic tachycardia as can be seen in inappropriate sinus tachycardia and POTS." (*Id.* at 53.)

On July 6, 2015, petitioner saw pediatric gastroenterologist Dr. Salim Hommeida for evaluation of her abdominal pain. (Ex. 22, p. 12.) Petitioner reported that her abdominal pain occurred every day lasting for a few hours on the right and left sides of her abdomen. She characterized the pain as "stabbing," and gauged the severity as a 7/10. (*Id.*) Petitioner also reported that she experienced nausea every day, and vomited once or twice per month roughly 30 minutes to an hour after eating. (*Id.*) Petitioner believed that her GI symptoms were related to her migraines. (*Id.*) Petitioner underwent CBC, CMP, ESR CRP, celiac disease cascade, and TSH testing all of which were unremarkable. (*Id.* at 13.) Dr. Hommeida noted that petitioner's tilt table test conducted by Dr. Fischer was suggestive of POTS. (Ex. 22, p. 13.) Dr. Hommeida also explained that petitioner's GI symptoms used to be associated with exacerbations of petitioner's migraine headaches, and therefore, abdominal migraine was a "likely etiology." (*Id.*) Dr. Hommeida ordered a gastric emptying study to evaluate for gastroparesis. (*Id.*)

Petitioner also received a psychological consult from Dr. Daniel R. Hiliker on July 6, 2015. (Ex. 34, p. 25.) Dr. Hiliker noted that petitioner had "some predisposition toward anxiety and worry and has struggled with more mood-related difficulties as her symptoms have persisted." (*Id.* at 26.) Dr. Hiliker recommended a variety of techniques for petitioner to manage her anxiety and worry, but did not make any clinical diagnoses. (*Id.*)

On July 7, 2016, petitioner was seen by nurse practitioner Bernice M. Casella. (Ex. 22, p. 1.) Petitioner reported that two weeks following her HPV vaccine she "developed frequent headaches, nausea, lightheadedness, dizziness, and multiple joint pains." (*Id.*) Petitioner reported that at the time of her visit, she was experiencing headaches four times per week, beginning in the right temporal area and radiating across her forehead. (*Id.*) Petitioner described the pain as a "clamp" and rated it at a 7

or 8/10. (*Id.*) Petitioner noted that her fibromyalgia medication had been effective in managing her joint pain but failed to help with her headaches. (*Id.* at 2.) Petitioner was still experiencing painful, burning rashes on her lower extremities roughly three times per year, and was unable to identify any specific triggers. (*Id.*) NP Casella noted that petitioner's autonomic reflex screen "revealed the presence of tachycardia and POTS," and suggested that a beta blocker could be effective in targeting petitioner's headache and autonomic symptoms. (*Id.* at 3.) Due to petitioner's family history of aortic defect, NP Casella recommended an ECG in order rule out any serious underlying cardiac abnormalities. (*Id.*) Additionally, NP Casella discussed retrials of past abortive medications and adding iron, riboflavin, and magnesium supplements to petitioner's diet. (*Id.* at 3-4.)

The following day, petitioner attended a group education session on autonomic dysfunction led by Registered Nurse Kay M. Comisky at Mayo Clinic. Petitioner was educated on techniques and lifestyle changes intended to manage her autonomic dysfunction focusing on diet, exercise, medications, interpersonal relationships and sleep hygiene. (Ex. 34, pp. 16-17.) Petitioner underwent an echocardiogram the same day, the results of which were normal apart from a slightly elevated diastolic blood pressure (roughly 4 points over normal) and slightly elevated pulmonary valve peak velocity (0.1 points over normal). (*Id.* at 18-20.)

Petitioner saw Dr. Fischer for a follow up exam on July 9, 2015. (Ex. 22, p. 10.) She noted that she had not experienced any headaches during the week, but that she had been a bit tired. (*Id.*) Dr. Fischer noted that petitioner "[did] have [POTS]" and directed her to increase fluid and salt intake to combat the tachycardic effects of the condition. (*Id.*) Dr. Fischer directed petitioner to begin an aerobic exercise program and prescribed metoprolol. (*Id.*) Additionally, Dr. Fischer noted that petitioner's test results indicated some cardiac deconditioning showing a decreased maximum oxygen uptake and a very slow return to normal heart rate following exercise. (*Id.* at 10-11.) Dr. Fischer also noted petitioner's low PCO2 levels with exercise, which he believed suggested petitioner was "trying too hard" and recommended cognitive behavioral therapy and relaxation techniques. (*Id.* at 11.) He also noted petitioner's low ferritin levels and recommended iron supplements. (Ex. 22, p. 11.) Finally, Dr. Fischer ordered a gastric emptying study due to "concerns about gastric emptying" and referred petitioner to RN Jeannie E. Clark for an individual treatment plan for POTS education. (*Id.*; *see also* Ex. 34, pp. 12-13.)

On August 7, 2015, petitioner emailed Dr. Fischer explaining that after returning home from a day out with friends she experienced elevated heart rate and vision changes which kept her up for "about an hour longer" than she had intended. (Ex. 34, p. 11.) Dr. Fischer explained that these symptoms were due to petitioner's "sensitive system" and more likely to occur when her medication had worn off; a sign that her medication is working. (*Id.*)

Petitioner reported to the Children's Hospital of Omaha ED on August 17, 2015, with a chief complaint of chest pain, abdominal pain, and difficulty breathing. (Ex. 33, p.

255-56.) Petitioner noted that she was developing a headache, although not a traditional migraine. (*Id.* at 256.) Petitioner's EKG was unremarkable. Her bowels were diffusely tender to palpation. (*Id.*) Petitioner's physical exam revealed appetite change, activity change, and fatigue, in addition to cough, chest tightness, and nausea. (*Id.* at 257.) Petitioner received an IV bolus of saline and slowly improved. (*Id.* at 258.) Petitioner was not given any medication for her headache and was discharged the same day. (*Id.*)

Petitioner emailed Dr. Fischer on August 24, 2015. (Ex. 34, p. 9-10.) She explained that her abdominal pain had become "much worse, making it difficult to eat regularly and difficult to keep food down." (*Id.* at 9.) She also explained that she visited a GI doctor on August 18 and that she underwent a gastric emptying study on August 20. (*Id.* at 9-10.) Petitioner recounted her ED visit on August 17, noting that it was suggested she undergo regular saline infusions and that she always felt better after saline IVs. She also explained that she had been experiencing a "sharp stabbing pain" in her left eye about once a day for a few seconds to several minutes since August 16. (*Id.* at 10.) Dr. Fischer responded explaining that the gastric emptying results should help make further treatment plans, and warning against infections and blood clots associated with regular saline infusions. (*Id.* at 9.) Dr. Fischer believed that petitioner's new eye pain was a new manifestation of her current blood flow and pain issues. (*Id.*)

Petitioner's gastric emptying study returned with normal results on August 26, 2015. (Ex. 34, p. 8.)

On September 2, 2015, petitioner's mother sent an email to Dr. Fischer recounting petitioner's new onset of daily brief eye pain with redness. (Ex. 34, p. 7.) She explained that petitioner's pain began in her left eye and had moved to her right eye and questioned if it could be related to her POTS medication. (*Id.*) Petitioner's mother also noted that petitioner had been complaining about a pain in the back of her head which was different from her typical headaches. (*Id.*) Petitioner had been experiencing daily nausea and stomach pain, and in light of the normal gastric emptying study, petitioner's mother asked if a gall bladder scan would be beneficial. (*Id.*) Dr. Fischer responded on the same day, explaining that he did not believe petitioner's abdominal pain was related to her gall bladder, nor did he believe that her eye pain was related to her medication. (*Id.* at 6-7.) Dr. Fischer did note, however, that petitioner's eye redness was of concern to him, and recommended that petitioner see an ophthalmologist. (Ex. 34, p. 6.) Ultimately, Dr. Fischer recommended that petitioner carry on with her current treatment plan and give it time to take effect. (*Id.* at 6-7.)

Petitioner returned to Dr. Weiland for the first time since her POTS diagnosis on September 8, 2015. (Ex. 31, p. 21.) Petitioner described her current medications and noted that IV saline tended to provide relief of her symptoms. (*Id.*) Dr. Weiland prescribed monthly saline infusions to evaluate the effectiveness of the treatment, and recommended a neurologist follow up once petitioner turned eighteen. (*Id.* at 22.)

On June 30, 2016, petitioner was seen by neurologist Dr. Pariwat Thaiseetthawatkul for further treatment of her POTS. (Ex. 39, p. 1.) Petitioner reported the same signs and symptoms as she had in her most recent examinations, but now included symptoms of brain fog, difficulty speaking with her migraine, some change in taste, constipation, and rectal bleeding. (Ex. 41, p. 4.) Petitioner's physical exam was normal, and Dr. Thaiseetthawatkul noted that petitioner needed blood and urine tests to clarify that she had POTS. (*Id.* at 5.) Dr. Thaiseetthawatkul scheduled bloodwork and urinalysis, recommended that petitioner continue to maintain an adequate diet of fluids and salt, avoid heat, vigorous exercises, and large meals, and monitor her blood pressure and heart rate. (*Id.* at 6.)

Petitioner began attending neurologic rehabilitation at Illinois Neuro & Physical Rehab on July 21, 2016. (Ex. 42, p. 10.) Petitioner noted that her symptoms began suddenly in July of 2012, and had occurred to some extent every day since. (*Id.* at 14.) Petitioner reported that exercise would sometimes help with body pain, while triggering other pains, that lack of sleep tended to coincide with "lots of pain," and that excessive sound or light led to migraines. (*Id.*) Petitioner listed a variety of previously reported and new symptoms on her intake forms.[6] Petitioner's initial exam included various stability tests revealing mild to severe reduction in stability with eyes closed and in different head positions. (*Id.* at 89.) Petitioner also underwent a Videonystagmography ("VNG") at her initial visit. (*Id.*) Petitioner's VNG results showed that she was "essentially stable" to "stable" under all conditions. (*Id.*)

While visiting Illinois Neuro & Physical Rehab, petitioner was seen twice per day by Dr. George Michalopoulos from July 25, 2016, to August 6, 2016. (*See* Ex. 42, pp. 65-87.) During these visits petitioner underwent oxygen therapy, complex cross crawls, chiropractic adjustments, parasympathetic stimulation, and convergence and divergence with beads. (*Id.*) Petitioner's symptoms improved throughout her rehab with few headaches, and rare abdominal pain and body or joint aches. (*Id.*)

On July 29, 2016, Dr. Thaiseetthawatkul informed petitioner's mother that petitioner's June 30 lab results were normal and confirmed her POTS diagnosis. (Ex. 41, p. 8.)

Petitioner returned to Dr. Thaiseetthawatkul on November 3, 2016, to follow up on her POTS. (Ex. 47, p. 4.) Dr. Thaiseetthawatkul noted that petitioner was "stable" and felt less dizzy but had occasional blackouts. (*Id.*) During this visit Dr. Thaiseetthawatkul noted that petitioner did not have orthostatic tachycardia. (*Id.*) Dr. Thaiseetthawatkul reviewed POTS with petitioner and emphasized limiting her physical activity to low-level exercise while maintaining adequate water and salt intake. (*Id.* at 5.)

Although petitioner was seemingly managing her POTS symptoms, she was still experiencing "fleeting, but frequent rashes" and non-specific myalgias. (Ex. 48, p. 5.)

[6] New symptoms included arthritis, chills, cold extremities, hallucinations, heat or cold intolerance, hot flashes, and weight gain. (Ex. 42, p. 16.)

Petitioner saw Dr. Roger Kobayashi on June 27, 2018, for concerns regarding mast cell disorder related to these symptoms. (*Id.*) Dr. Kobayashi ordered bloodwork and other labs to evaluate for mast cell activation syndromes, however petitioner has not filed any additional documentation regarding the results of these tests. (*Id.* at 16.)

Petitioner has not filed any additional medical records.

b. As Reflected in Petitioner's Declaration

Petitioner filed her declaration on January 9, 2017. (ECF No. 40.) Petitioner received her HPV vaccine on July 19, 2012. (*Id.* at 1.) Prior to her vaccination, she experienced occasional minor headaches "but they were nowhere near the horrible migraine pain that [she] experienced after [her] third shot of Gardasil." (*Id.*) Petitioner noted that after her third Gardasil shot, she "started to get migraines that ached and throbbed, located on the top right side of [her] head, around the hairline, which [she continues] to experience up to the date of this affidavit." (*Id.* at 2.) Petitioner explained that she was prescribed migraine medication by her family practice doctor, but that it was ineffective and led her to seek treatment by a neurologist who prescribed "overwhelming amounts of medication, but most made me feel worse, and the slight few that did provide relief only did so for a short while." (*Id.* at 2-3.)

Petitioner describes new symptoms of "chest pain, stronger fatigue, body pain every way, bruising, rashes, blurred vision, blacking out vision, stomach pain, nausea, tightness of breath, more extreme migraines, numbness and tingling, inability to sleep, and rapid heart rate," beginning in early 2013. (ECF No. 40, p. 3.) She describes her admission to the Children's Hospital in Spring of 2013 but notes that the treating physicians could not find a cause for her symptoms. (*Id.*) Petitioner then explains that since her first admission to the Children's Hospital, she has seen new doctors, been prescribed new medications, and visited the emergency room many times all with no explanation of her symptoms. (*Id.*) She notes that "[m]ost of [her] doctors came to the conclusion that [her condition] was all in [her] head, somehow related to anxiety." (*Id.*)

Petitioner notes that she received her POTS diagnosis at the Mayo Clinic in 2015 after undergoing several tests with Dr. Fischer. (ECF No. 40, p. 4.) Following this diagnosis, petitioner notes that she was prescribed a beta blocker to lower her heart rate, but still suffers from the symptoms described above. (*Id.*) She explains that despite her new diagnosis and prescription, she still found it "extremely difficult to get out of bed every morning due to all [her] aches and pains." (*Id.*) She continued to seek treatment at the emergency room and from different doctors during this period as well. (*Id.*) Petitioner notes that her abdominal pain and nausea worsened, and that in early 2016, she began to feel intense abdominal pain correlating with her menstrual cycle. (*Id.*) Petitioner explains that she saw an OB/GYN for this pain, but after an examination and ultrasound, nothing was found. She was prescribed birth control pills to reduce her pain. (*Id.*)

After graduating from high school in May 2016, petitioner spent two weeks at the Illinois Neuro and Physical Rehabilitation Clinic. She explained that her treatment generally involved chiropractic adjustments and exercises, and that the treatment left her feeling better than she had during the past four years. (ECF No. 40, p. 5.)

Petitioner explained that she continued to see a POTS specialist in her hometown. She notes that she still suffers from migraines about once or twice per week, and has had to miss college classes to visit the emergency room for her migraine and chest pain. (*Id.* at 6.) She continues to suffer from "fatigue, chest pains, stomach pains, nausea, numbness and tingling, tightness of breath, body pain, joint pain, rapid heart rate, blurred vision and occasional loss of vision." (*Id.*) She explained that she was seeing a functional neurologist every week that provided temporary relief. (*Id.*) Although she notes that she has seen some improvement, petitioner concludes her affidavit by noting she continues to suffer from her symptoms. (*Id.*)

c. As Reflected in Petitioner's Testimony

Petitioner also testified at the hearing held on June 9, 2021. Petitioner stated that she was a healthy child. (Tr. 10.) Petitioner began playing soccer at age four and began running track and field in seventh grade at age twelve. (*Id.* at 11.) She recalled enjoyed spending time outside and participating in sports. (*See id.*) She testified that she occasionally experienced headaches related to her allergies when she was in middle school. (*Id.* at 12.) She indicated that the headaches did not interfere with her activities. (*Id.* at 12-13.) She also recalled attending school, taking difficult classes, and receiving mostly A's prior to receiving the HPV vaccine at issue. (*Id.* at 13-14.)

After receiving the first two doses of Gardasil in 2011, petitioner recalled being hesitant to receive a third dose due to pain and a burning sensation at the injection site. (Tr. 14-15.) On July 19, 2012, the date petitioner received the third Gardasil vaccine, petitioner testified that she was in good health, though she acknowledged that the medical record from that visit lists headache as a complaint. (*Id.* at 15-16.) She testified that Dr. Weiland gave her a release to participate in school athletic activities during her encounter on July 19, 2012. (*Id.* at 20 (citing Ex. 31, p. 208).)

A few weeks after receiving the third Gardasil shot, petitioner testified that she began experiencing "different kinds of headaches on the top of [her] head that were very painful." (Tr. 16.) She elaborated that the headaches were localized to the top of her head, along the hairline on the right side. (*Id.* at 17.) Petitioner differentiated these headaches from the headaches she experienced prior, noting that her allergy-related headaches were limited to the front of her forehead and behind her eyes. (*Id.* at 17, 29.) She explained that her allergy-related headaches go away with allergy medication. (*Id.* at 29.) She also noted that the headaches she experienced after the Gardasil shot were "more severe and painful" and were "stopping [her] from being able to participate in activities that [she] had loved prior to that, including soccer, school, and track." (*Id.* at 17.) She described the new headaches as a throbbing pain with pressure and testified that they prevented her from getting out of bed at times and made her avoid bright lights

and loud sounds. (*Id.* at 29.) Petitioner testified that she began missing soccer practice due to her headaches. (*Id.* at 18.)

Petitioner recalled visiting Dr. Weiland to address her headaches and fatigue in October 2012. (Tr. 21.) Prior to her third Gardasil shot, petitioner testified that she always had a lot of energy. (*Id.* at 21, 23.) However, in addition to the headaches, petitioner remembered experiencing fatigue at the time of her visit with Dr. Weiland. (*Id.*) Around this time, petitioner began missing soccer practice, which prompted her to see Dr. Weiland. (*Id.* at 21-22.) She testified that her fatigue began around the end of July of 2012. (*Id.* at 22.) Petitioner also testified that she began to struggle with school attendance, studying, and socializing with friends. (*Id.* at 23.) She quit soccer in December 2012 after her symptoms continued. (*Id.* at 34.) She also recalled having to quit her school's marching band due to her health. (*Id.* at 24.)

Regarding her initial treatment, petitioner recalled taking indomethacin for pain. (Tr. 25.) She testified that the indomethacin helped but did not completely relieve her pain. (*Id.*) She remembered taking multiple visits to the emergency room for her headaches. (*Id.* at 26.) Prior to July of 2012, petitioner had not visited the emergency room. (*Id.*)

Petitioner testified that she visited the Children's Hospital emergency room on April 30, 2013, because her headaches were preventing her from attending school and interfering with activities of daily life. (Tr. 26-27.) She remembered undergoing extensive testing to determine the cause of her headaches. (*Id.* at 28.) She recalled being diagnosed with tachycardia during this hospital visit. (*Id.* at 30.)

After her hospital stay, petitioner testified that she began seeing Dr. Kugler. (Tr. 31.) Dr. Kugler gave petitioner a Holter monitor to wear for about a week. (*Id.* at 31-32.) She recalled Dr. Kugler calling her to tell her that her heart rate was abnormally high. (*Id.* at 32.) At this time, petitioner was struggling with headaches and fatigue. (*Id.* at 33.)

In May of 2013, petitioner testified that she was missing a lot of school. (Tr. 33.) She testified that she tried to be more involved in extracurricular activities but had to quit a school play because of her fatigue and pain. (*Id.*) She was not participating in sports at this time. (*Id.*) Petitioner's symptoms continued through the summer and the following school year. (*Id.* at 34-35.)

Due to her ongoing and worsening symptoms, petitioner sought care from multiple doctors. (Tr. 35.) Petitioner recalled some doctors suspecting that her symptoms were related to stress or anxiety. (*Id.* at 36.) However, petitioner did not remember any reason she would be feeling stress or anxiety. (*Id.*) She testified that she enjoyed school and challenging herself. (*Id.*) Petitioner recalled seeing neurologists Dr. Whyte and Dr. Nelson. (*Id.*) Dr. Whyte prescribed her Depakote, which she claimed provided "slight relief." (*Id.* at 36-37.) However, the "relief went away shortly after beginning the medication." (*Id.* at 37.)

In early 2015, petitioner's mother began to suspect that the third Gardasil shot triggered petitioner's condition. (Tr. 37.) Petitioner then traveled to the Mayo Clinic to see Dr. Fischer and determine the cause of her symptoms. (*Id.* at 38.) Around this time, petitioner had begun experiencing joint pain, body pain, exhaustion, [and] nausea" as well as "extreme brain fog or the inability to focus." (*Id.* at 38-39.) She also recalled times when her vision would blackout or become blurry. (*Id.* at 39.) Based on her symptoms and test results, Dr. Fischer diagnosed petitioner with POTS. (*Id.* at 39-40.) Dr. Fischer prescribed petitioner with metoprolol for her elevated heart rate and suggested increasing her salt intake. (*Id.* at 40.)

Petitioner testified that her symptoms continued after her visit to Dr. Fischer, and at the time of the hearing, she was still experiencing headaches. (Tr. 40-41.) Although the headaches have become less severe, they still interfere with activities and have caused her to occasionally miss work as a school librarian. (*Id.* at 41.)

IV. Expert Opinions

a. Petitioner's Expert, Svetlana Blitshteyn, M.D.

Petitioner offered an expert opinion from neurologist and autonomic specialist Dr. Svetlana Blitshteyn to support her claim. Dr. Blitshteyn is certified by the American Board of Psychiatry and Neurology. (Ex. 45, p. 1.) She received her medical degree from State University of New York School of Medicine and Biomedical Sciences in 2002. (*Id.*) She completed her internal medicine residency at State University of New York at Buffalo and her neurology residency at Mayo School of Graduate Medical Education. (*Id.*) She served as staff neurologist at Kinkel Neurologic Center in Williamsville, New York from 2007 to 2009, and as an attending neurologist at The Brain and Spine Center in Buffalo, New York from 2010 to 2011. (*Id.*) Dr. Blitshteyn currently serves as an Intra-operative monitoring neurologist at Buffalo Synapse, and as the Director and Founder of Amherst Neurology and Dysautonomia Clinic. (*Id.*) Additionally, she currently works as a clinical assistant professor at the department of neurology for the State University of New York at Buffalo School of Medicine and Biomedical Sciences. (*Id.*) Dr. Blitshteyn has published several different pieces of medical literature on neurologic and autonomic disease. (*Id.* at 5-6; *see also* Tr. 53.)

Dr. Blitshteyn maintained that the correct diagnosis for petitioner is POTS. Dr. Blitshteyn opined that "[petitioner's] symptoms of headache, difficulty concentrating, tachycardia, palpitations and inability to maintain her school work and engage in her previous activities, such as soccer, were all caused by POTS from the onset." (Ex. 44, p. 3.) She explained that "POTS is a heterogenous disorder of the autonomic nervous system characterized by orthostatic tachycardia, symptoms of exercise and orthostatic intolerance, and non-orthostatic symptoms, such as weakness, fatigue, and lightheadedness." (*Id.* (citing Mark J. Thieben et al., *Postural Orthostatic Tachycardia Syndrome: The Mayo Clinic Experience*, 82(3) MAYO CLINIC PROC. 308 (2007) (Ex. 44-1)); Tr. 63-64.) She elaborated that "patients with POTS have significant difficulty

standing, walking, and exercising." (*Id.*; Tr. 63-64.) She further stated that "headache is the most common comorbidity in POTS." (Tr. 64.) Dr. Blitshteyn identified viral infection, surgery, pregnancy, trauma, and vaccinations as potential triggers of POTS. (Ex. 44, p. 3 (citing Thieben et al., *supra*, at Ex. 44-1; Svetlana Blitshteyn, *Postural Tachycardia Syndrome Following Human Papillomavirus Vaccination*, 1 EURO. J. NEURO. 135 (2013) (Ex. 44-2)); *see also* Tr. 65 (noting that the etiology for POTS is multifactorial).

According to Dr. Blitshteyn, a person must meet three criteria to be diagnosed with POTS. (Tr. 64, 117.) First, "postural tachycardia must be present on a tilt-table test or a stand test." (*Id.*) Second, the person must have a drop in blood pressure or orthostatic hypotension when standing. (*Id.*; *see also* Ex. 44, p. 3 (explaining that upon assuming an upright position, individuals with POTS will experience a drop in blood pressure). Finally, the person must exhibit symptoms of orthostatic intolerance for at least three to six months. (Tr. 64, 117.) Dr. Blitshteyn noted that petitioner's abnormal tilt-table test and ten-minute stand test performed by Dr. Fischer and reviewed by Dr. Low support a POTS diagnosis. (*Id.* at 117-19.) Based on petitioner's autonomic testing by Dr. Fischer and Dr. Low and petitioner's symptoms of headache, fatigue, exercise intolerance, and abnormally high heartrate, Dr. Blitshteyn concluded that petitioner satisfied the diagnostic criteria for POTS. (*Id.* at 110-11, 114-19.)

Regarding Dr. Gibbons's contention that petitioner does not suffer from POTS due to her inconsistent heartrate elevations, Dr. Blitshteyn explained that "there is no diagnostic criteria that requires a patient to have consistently present postural tachycardia by precisely 40 bpm every time the patient has a bedside vital signs measurement." (Ex. 46, p. 1; *see also* Tr. 125 (stating that "[t]here is no criteria for consistent and repeated heart rate elevations from the American Autonomic Society consensus statement").) She noted that "on some days, [POTS] patients will have more normal heart rate, like [petitioner] did [at the] Mayo clinic where supine heart rate was 90 instead of 111." (Tr. 125.) She continued that "[t]he diagnostic criteria for POTS requires a 40 bpm heart rate elevation from supine to standing, either within 10 min[utes] of tilt table test OR standing test in a teenager." (Ex. 46, p. 1.) According to Dr. Blitshteyn, petitioner's documented heart rate elevation from 90 bpm supine to 130 bpm standing during Dr. Fischer's stand test satisfies the diagnostic criteria even without additional test results. (*Id.*; Tr. 117-18; *see also* Ex. 34, p. 40.) Significantly, Dr. Blitshteyn also noted that petitioner's POTS diagnosis was confirmed by Drs. Fischer, Low, and Thaisettawatkul. (Ex. 46, p. 2.) Dr. Blitshteyn noted that Drs. Low and Fischer are both POTS experts from the Mayo Clinic, and that Dr. Thaisettawatkul trained at the Mayo Clinic. (*Id.*; *see also* Tr. 49, 93, 117 (testifying that Dr. Low set up the autonomic lab at the Mayo Clinic and that Dr. Fischer runs a POTS clinic for teenagers at the Mayo Clinic). She concluded that based on her own opinion, and the opinion of three other highly credible experts, petitioner's POTS diagnosis is "irrefutable." (Ex. 46, p. 2; Tr. 116.)

With respect to Dr. Gibbons's contention that petitioner's medications may have skewed her autonomic test results, Dr. Blitshteyn explained that petitioner was not

taking trazadone or amitriptyline at the time of her testing at the Mayo Clinic. (Ex. 46, p. 2.) However, she conceded at hearing that the medical records indicate that petitioner was on Savella at that time and that Savella can increase heartrate both supine and standing. (Tr. 120-21.) However, Dr. Blitshteyn explained that petitioner was not taking trazadone, amitriptyline, or Savella when she was wearing her Holter monitor, but was taking propranolol, a medication used to treat POTS and reduce heart rate. (Ex. 46, p. 2; Tr. 74-75, 121.) During this test, despite petitioner's medication used to lower her heart rate, she was still observed to show an elevated heartrate range of 54-183 bpm. (Tr. 74-75, 121.) Dr. Blitshteyn also noted that if Dr. Low or Dr. Fischer believed that petitioner's use of Savella was significant, they would have so indicated. (*Id.* at 121-22.) Thus, Dr. Blitshteyn concluded, it is "undeniable that petitioner's tachycardia is not secondary to medication side effects," because it occurred when petitioner was no longer taking the medication at issue and even when she was taking medication specifically prescribed to reduce her heart rate. (Ex. 46, pp. 2-3.)

Dr. Blitshteyn also addressed petitioner's QSART results, opining that petitioner's reduced response in her forearm and low normal output in her proximal leg and foot are results often present in patients with POTS and/or small fiber neuropathy ("SFN"). (Ex. 46, p. 5; *see also* Tr. 368.) Further, in Dr. Blitshteyn's experience, SFN occurs in about 50% of POTS patients. (Ex. 46, p. 5; Tr. 368.) Dr. Blitshteyn opined that petitioner also experienced SFN, which would explain her muscle and joint pain. (Ex. 46, p. 5.) Dr. Blitshteyn cited a large case series of pediatric patients with unexplained chronic pain syndrome who also showed mild abnormalities on QSART. (*Id.* (citing Anne Louise Oaklander & Max M. Klein, *Evidence of Small-Fiber Polyneuropathy in Unexplained Juvenile-Onset, Widespread Pain Syndromes*, 131(4) PEDIATRICS E1091 (2013) (Ex. 46-14)).) Dr. Blitshteyn concluded that petitioner would "qualify for possible SFN, at the very least." (*Id.*) Dr. Blitshteyn also noted that in the Oaklander & Klein case series, many patients had positive autoimmune markers and 80% of patients with idiopathic chronic pain syndrome improved with immunomodulatory therapy. (*Id.* (citing Oaklander & Klein, *supra*, at Ex. 46-14).)

In response to Dr. Gibbons's contention that deconditioning is a more likely cause of petitioner's symptoms, Dr. Blitshteyn indicated that petitioner's deconditioning was secondary to POTS, not an independent cause of her orthostatic symptoms. (Tr. 311-13; Zosia Chustecka, *Case reports of 'syndrome' appearing after HPV vaccination,* MEDSCAPE, https://www.medscape.com/viewarticle/851186#vp_2 (Sept. 18, 2015) (Ex. 44-3).) She further noted that most POTS patients are not as active, resulting in deconditioning. (Tr. 311-13.) However, during oral testimony, Dr. Blitshteyn conceded that a diagnosis of POTS requires at least six months of orthostatic symptoms "that occur in the absence of prolonged bedrest or deconditioning . . . ." (*Id.* at 301-02 (quoting Chustecka, *supra,* at Ex. 44-3, p. 3).) Additionally, Dr. Blitshteyn stated that deconditioning does not cause POTS or inappropriate sinus tachycardia ("IST"). (Tr. 102.) While she noted that deconditioning may cause an increase in heart rate, this heart rate would not exceed pathological levels of 95 bpm over a period of years. (*Id.*)

Furthermore, Dr. Blitshteyn opined that petitioner's elevated resting heart rate was consistent with IST, a rare autonomic dysfunction that can coincide with POTS.[7] (Tr. 80-81, 104-05.) Patients with IST have a dysfunction of the heart's sinoatrial node, which controls the heart rate. (*Id.* at 81.) Dr. Blitshteyn contended that Dr. Low diagnosed petitioner with IST in July 2015 when interpreting her autonomic testing. (*Id.* at 81-82, 92-93 (citing Ex. 34, p. 53) (Dr. Low noting that "[t]here is resting and symptomatic orthostatic tachycardia as can be seen in inappropriate sinus tachycardia with POTS").) She further opined that petitioner had IST in April 2013, as evidenced by her heart monitor tests showing an elevated heart rate. (*Id.* at 82-83 (Dr. Blitshteyn noting that petitioner's hospital heart rate reading on April 30, 2013, and her Holter monitor results from May 2013 were both consistent with IST, which was later confirmed by Dr. Low).)

Regarding causation, Dr. Blitshteyn identified autoimmunity as a factor in causing POTS. (Ex. 44, p. 3; Tr. 65.) Dr. Blitshteyn explained that "POTS has been viewed as a limited form of the autoimmune autonomic ganglionopathy and neuropathy." (Ex. 44, p. 3.) She noted that "various antibodies have been identified in patients with POTS, with the first one being identified as acetylcholine receptor ganglionic neuronal (ganglionic AchR) antibody." (*Id.* (citing Thieben et al., *supra*, at Ex. 44-1; Steven Vernino et al., *Invited Article: Autonomic Ganglia: Target and Novel Therapeutic Tool*, 70 NEURO. 1926 (2008) (Ex. 44-6)); Tr. 66.) Additionally, "[o]ther antibodies subsequently identified in patients with POTS include antibodies to cardiac proteins, to Beta-1/2-adrenergic, alpha 1-adrenerigc [*sic*] and M2/3 muscarinic receptors." (Ex. 44, p. 3 (citing Xiao-Li Wang et al., *Autoimmunoreactive IgGs from Patients with Postural*

[7] In his report, Dr. Low had indicated that petitioner had "resting and symptomatic orthostatic tachycardia as can be seen in inappropriate sinus tachycardia with POTS." (Ex. 34, p. 53.) During the hearing, petitioner's counsel asked Dr. Blitshteyn about the diagnostic criteria for IST. (Tr. 83.) Respondent's counsel objected to the introduction of a new injury. (Tr. 84, 105.) Respondent contended the reference to IST in the medical record was "offhand" and not a formal diagnosis. (Tr. 87-88.) In response to respondent's objection, petitioner' counsel indicated that "we're not proposing to do any of those things" and that "[w]e're proposing to have an expert explain the medical record." (Tr. 88.) I reserved judgment on the issue. (Tr. 90.) Subsequently, Dr. Blitshteyn testified that Dr. Low's record constituted a diagnosis of POTS as well as a separate diagnosis of IST. She additionally contended the IST was evidenced as far back as petitioner's 2013 cardiac testing. (Tr. 92-93.) Later, she interpreted Dr. Lows' record as characterizing petitioner as having a unified autonomic disorder described as "POTS with IST." (Tr. 107.) Asked on cross-examination whether she was offering an opinion that petitioner's HPV vaccine caused IST, she characterized the IST as a "finding" rather than a separate diagnosis. (Tr. 212.) She indicated of POTS and IST that "you can't really separate them out" and that "[w]e are going by POTS, because POTS is well known. (Tr. 212.) Asked specifically if her opinion "is limited to the HPV vaccine caused POTS" she responded "[t]hat is fine to think of it this way . . . ." (Tr. 212-13.) Consistent with this, petitioner's post-hearing brief characterizes her claim as follows: "Ms. [F.] claims the aforesaid vaccination more likely than not caused her to develop POTS, with the onset of the injury taking place within two weeks post-vaccination in or about July 2012." (ECF No. 118, p. 2.) However, petitioner continues to maintain that IST constitutes a separate "overlap[ping]" form of autonomic dysfunction. (*Id*. at 19.) In the analysis below, I address whether there is preponderant evidence that petitioner experienced tachycardia dating as far back as petitioner alleges and, therefore, whether it could constitute evidence of petitioner's alleged autonomic disorder, which petitioner and Dr. Blitshteyn both agree can be characterized as POTS. However, given the record as a whole, I clarify that petitioner has not presented a claim based on IST alone.

Orthostatic Tachycardia Syndrome, 6 PROTEOMICS CLIN. APPL. 615 (2012) (Ex. 44-7); Hongliang Li et al., *Autoimmune Basis for Postural Tachycardia Syndrome,* 3 J. AM. HEART ASS'N 2 (2014) (Ex. 44-8)); *see also* Tr. 133-34 (citing Li et al., *supra*, at Ex. 44-8) (Dr. Blitshteyn asserting that the Li et al. rabbit study provides evidence "that there is activity of the adrenergic antibodies in patients with POTS").)

Dr. Blitshteyn noted that adrenergic antibodies and muscarinic antibodies are important to the autonomic nervous system. (Tr. 66.) Dr. Blitshteyn conducted her own study of 100 patients with POTS and found that "25% had positive ANA, 7% had at least one positive anti-phospholipid antibody and 3% had elevated tissue transglutaminase; one in 3 had a co-morbid autoimmune disorder at a prevalence higher than in [the] general population." (Ex. 44, p. 3 (citing Svetlana Blitshteyn, *Autoimmune Markers and Autoimmune Disorders in Patients with Postural Tachycardia Syndrome (POTS)*, LUPUS 1 (2015) (Ex. 44-9)).) Based on these findings, Dr. Blitshteyn concluded that "[t]he identification of antibodies in the serum of patients with POTS, in conjunction with clinical history of onset after a viral illness or vaccination, provides substantial evidence of the autoimmunity as a cause of POTS in many patients including [petitioner]." (*Id.* (citing Shani Dahan et al., *Postural Orthostatic Tachycardia Syndrome (POTS) – A Novel Member of the Autoimmune Family,* 25 LUPUS 339 (2016) (Ex. 44-10)).)

Significantly, Dr. Blitshteyn also identified a recent study by Hineno et al. as evidence of the association of antibodies and autoimmunity with post-vaccination POTS. (Tr. 127, 130, 157-59 (citing Akiyo Hineno et al., *Autoantibodies Against Autonomic Nerve Receptors in Adolescent Japanese Girls After Immunization with Human Papillomavirus Vaccine*, 2(2) ANN. ARTHRITIS CLIN. RHEUMATOL. 1014 (2019) (Ex. 50)).) She elaborated that the Hineno et al. study shows "that the prevalence of adrenergic antibodies or G coupled receptor antibodies were much higher than in those who were not vaccinated" and that antibodies are associated with autonomic disorders such as POTS. (*Id.*) Although she acknowledged on cross-examination that there is not substantial literature linking alpha 1 adrenergic receptor antibodies with POTS, she maintained that the Hineno et al. study shows a link between the HPV vaccine and these antibodies. (*Id.* at 214-15.)

Dr. Blitshteyn disagreed with Dr. Gibbons's assertion that finding an autoimmune basis for POTS is "not the general experience among experts in the field." (Ex. 46, pp. 4-5.) She noted that the references Dr. Gibbons provided were authored in 1999, 2009, and 2013. (*Id.*) She explained that "most experts agree that POTS has an autoimmune basis in at least a significant subset of patients, specifically in those whose POTS began after vaccination." (*Id.* (citing Dahan et al., *supra*, at Ex. 44-10; Blitshteyn, *supra*, at Ex. 44-9; Artur Fedorowski et al., *Antiadrenergic Autoimmunity in Postural Tachycardia Syndrome*, 19 EUROPACE 1211 (2017) (Ex. 46-6); Mohammed Ruzieh et al., *The Role of Autoantibodies in the Syndromes of Orthostatic Intolerance: A Systematic Review*, 51 SCANDINAVIAN CARDIOVASCULAR J. 243 (2017) (Ex. 46-7); Rebecca E. Chandler, *Safety Concerns with HPV Vaccines Continue to Linger: Are Current Vaccine Pharmacovigilance Practices Sufficient?*, 40 DRUG SAF. 1 (2017) (Ex. 46-9)).) Dr. Blitshteyn also noted that there is an ongoing research study looking into the adrenergic

and muscarinic antibodies in patients with post-HPV vaccine POTS. (*Id.* (citing Chandler, *supra*, at Ex. 46-9).) Dr. Blitshteyn disagreed with Dr. Gibbons about the relevance of these antibodies, stating that "they are clinically relevant and have been reported in patients with post-HPV vaccine POTS and small fiber neuropathy." (*Id.* at 4-5 (citing Svetlana Blitshteyn & Jill Brook, *Postural Tachycardia Syndrome (POTS) with Anti-NMDA Receptor Antibodies After Human Papillomavirus Vaccination*, 65 IMMUNOL. RES. 1 (2017) (Ex. 46-10); Jeanne E. Hendrickson & Christopher A. Tormey, *Human Papilloma Virus Vaccination and Dysautonomia: Considerations for Autoantibody Evaluation and HLA Typing*, 34 VACCINE 4468 (2016) (Ex. 46-11); Jafar Kafaie et al., *Clinical and Laboratory Profiles of Idiopathic Small Fiber Neuropathy in Children: Case Series*, 19 J. CLIN. NEUROMUSC. DIS. 31 (2017) (Ex. 46-12); Jill R. Schofield & Jeanne E. Hendrickson, *Autoimmunity, Autonomic Neuropathy, and the HPV Vaccination: A Vulnerable Subpopulation*, CLIN. PED. 1 (2018) (Ex. 46-13)).)

Dr. Blitshteyn conceded that all of petitioner's autoimmune tests were negative for any disorders. However, she emphasized that American doctors do not test for adrenergic and muscarinic antibodies. (Ex. 44, pp. 4-5; Tr. 141-42.) Thus, Dr. Blitshteyn maintained her position that even though petitioner's autoimmune testing was negative for autoimmune processes, she did not undergo the test for relevant post-HPV vaccine antibodies that is unavailable in the United States. (Ex. 46, p. 5; Tr. 141-42.) Therefore, Dr. Blitshteyn argued that petitioner's normal autoimmune tests should not be regarded as evidence against an autoimmune process. (Ex. 46, p. 5.)

Regarding the specific mechanism by which the HPV vaccine can cause POTS, Dr. Blitshteyn opined that although the precise pathogenesis of new-onset POTS following HPV vaccination is still being investigated, the "most likely" mechanism is "molecular mimicry with cross-reacting antibodies against potential targets of the autonomic ganglia (i.e., AchR ganglionic neuronal antibody), neurons, cardiac proteins, Beta1/2-adrenergic, alpha 1 adrenergic or M2/3 muscarinic receptors." (Ex. 44, p. 4; Tr. 126-27.) Dr. Blitshteyn noted that Gardasil contains aluminum adjuvant, which is "a potent immune system stimulator." (Tr. 126-27.) She theorized that antibodies, such as alpha 1 adrenergic receptor, can cross-react with the aluminum adjuvant contained in the Gardasil vaccine to trigger POTS. (*Id.* at 155.) She also noted that "there is new evidence that patients with neurologic symptoms developed after Gardasil have abnormalities in the spinal fluid consistent with neuro-inflammation and neuro-immune process." (Ex. 44, p. 4.)

To support her theory, Dr. Blitshteyn cited a study of 32 patients with persistent neurologic symptoms following HPV vaccination, which found that each patient had "increased pro-inflammatory cytokines and antibodies to GluN2B-NT2, GluN2B-CT and GluN1-NT receptors compared to the healthy controls." (Ex. 44, p. 4 (citing Yukitoshi Takahashi et al., *Immunological Studies of Cerebrospinal Fluid from Patients with CNS Symptoms After Human Papillomavirus Vaccination*, 298 J. NEUROIMMUNOL. 71 (2016) (Ex. 44-21)).) A study of mice also found that the HPV vaccine may result in brain changes through anti-HPV antibodies that cross-reacted with the mouse brain protein. (*Id.* (citing Rotem Inbar et al., *Behavioral Abnormalities in Female Mice Following*

Administration of Aluminum Adjuvants and the Human Papillomavirus (HPV) Vaccine Gardasil, 65 IMMUNOL. RES. 136 (2017) (Ex. 44-22)).)

Dr. Blitshteyn also provided several case reports to bolster her theory. She cited a case series of six patients who developed POTS following a Gardasil vaccination. She explained that three of the patients also had abnormalities on QSART like petitioner, and also like petitioner, all six patients had significant headache, nausea, and fatigue. (Ex. 44, p. 4 (citing Thieben et al., *supra*, at Ex. 44-1.) Dr. Blitshteyn also cited larger case series from Japan, Denmark, Mexico, and Italy. (*Id.*) In the Japanese series, forty adolescent girls developed "various neurologic symptoms consistent with sympathetic dysfunction after HPV [vaccination]." (*Id.* (citing Tomomi Kinoshita et al., *Peripheral Sympathetic Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccine*, 53 INTERN. MED. 2185 (2014) (Ex. 44-13).) In Denmark, fifty-three patients reported onset of autonomic dysfunction following HPV vaccination. (*Id.* (citing Louise S. Brinth et al., *Orthostatic Intolerance and Postural Tachycardia Syndrome as Suspected Adverse Effects of Vaccination Against Human Papilloma Virus*, 33 VACCINE 2602 (2015) (Ex. 44-14)).) The patients in the Japanese and Danish case series developed symptoms like petitioner's, including "orthostatic dysregulation, fatigue, widespread pain, and significant functional impairment, such as inability to concentrate and participate in previous activities." (*Id.*) Dr. Blitshteyn further explained that in addition to her own case studies, a study by Dr. Low et al. also found that autonomic disorders may occur after immunization, and Dr. Yehuda Shoenfeld and his team of researchers specifically discuss post-vaccination POTS in a recent review article. (Ex. 46, p. 3 (citing Vernino et al., *supra*, at Ex. 44-6); Dahan et al., *supra*, at Ex. 44-10.)

Dr. Blitshteyn conceded that "the European Medical Agencies concluded in 2015 that there appears to be no evidence of increased prevalence of POTS and CRPS after HPV vaccines." (Ex. 46, p. 3.) She also acknowledged that there has not yet been a prospective randomized controlled study examining whether HPV immunization leads to a higher incidence of POTS and conceded that such a study is needed to establish causality. (*Id.*; *see also* Tr. 72 (stating that "[t]here is no conclusive evidence" that the HPV vaccine can cause POTS).) However, she maintained that "concerns regarding a possible association remain, due to a lack of randomized double-blinded controlled study that can conclusively and decisively address this question." (Ex. 46, p. 3 (citing Rebecca E. Chandler et al., *Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster of Reports in VigiBase*, 40 DRUG SAF. 81 (2017) (Ex. 44-19); Peter C Gøtzsche et al., *Complaint to the European Ombudsman over Maladministration at the European Medicines Agency (EMA) in Relation to the Safety of the HPV Vaccines*, COCHRANE NORDIC (2016) (Ex. 44-20)).)

Regarding timing, Dr. Blitshteyn opined that based on the medically acceptable timeframe for other post-vaccination neurological disorders, twelve weeks is the maximum time interval for onset of POTS following vaccination. (Tr. 217-18.) She explained that given the proposed pathological process involving autoimmunity via molecular mimicry, post-vaccination POTS should occur within three months of

vaccination. (*Id.*) She acknowledged that eight months would be too long to establish an appropriate temporal interval between vaccination and onset. (*Id.* at 218.)

Dr. Blitshteyn further opined that petitioner's onset of POTS occurred within two weeks of her third Gardasil vaccination, marked by severe headaches of a different character than her pre-vaccination headaches. (Tr. 197, 200, 203-04, 250.) Although she acknowledged variability in POTS cases, she asserted that two weeks was an appropriate timeframe for onset of POTS following vaccination. (*Id.* at 196, 199, 216.) Dr. Blitshteyn used the accepted timeframe for post-vaccination neurological disorders as a reference, noting that there are no studies demonstrating the appropriate interval for post-vaccination POTS. (*Id.* at 217-18.) While Dr. Blitshteyn conceded that petitioner experienced headaches prior to vaccination, she contended that petitioner's pre-vaccination headaches were never petitioner's chief complaint, and instead, secondary to allergy attacks, sinusitis, and tonsillitis. (Ex. 44, pp. 3-4.) Further, petitioner did not report that these headaches were severe or had any impact on functioning at school or as an athlete. (*Id.* at 4.) In comparison, Dr. Blitshteyn pointed out that petitioner's post-vaccination headaches were debilitating and caused petitioner to miss school and quit participating in athletics. (*Id.*)

Further, Dr. Blitshteyn noted that there is no record of petitioner having resting tachycardia prior to her HPV vaccination besides incidences of elevated heart rate associated with occasional childhood. (Ex. 46, p. 3.) Dr. Blitshteyn also noted that Dr. Gibbons contended that petitioner experienced resting tachycardia in 2008 with an elevated heartrate of 118 bpm, a time when petitioner was ten years old. (*Id.*) Dr. Blitshteyn explained that the resting heartrate for a 10-year-old is between 75 and 118 bpm, and therefore not abnormally high. (*Id.*)

With respect to Dr. Gibbons's contention that petitioner's symptoms did not arise until ten months after petitioner was vaccinated, Dr. Blitshteyn explained that petitioner's tachycardia symptoms could have arisen shortly after her vaccination, but that they could have simply gone undetected. (Ex. 46, p. 4; *see also* Tr. 199-200 (noting that there is typically a diagnostic delay in POTS cases).) To support this opinion, Dr. Blitshteyn noted that petitioner's tachycardia "was only revealed incidentally via a hospitalization for headache in May of 2013, which prompted a visit to Dr. Weiland on May 6, 2013." (Ex. 46, p. 4.) In Dr. Blitshteyn's experience with POTS patients, "it is quite common for teens with POTS to present with headaches or nausea or fatigue and be unaware of their heart rate or blood pressure." (*Id.*) Thus, Dr. Blitshteyn maintained that petitioner's disabling headaches that arose in July 2012 following her HPV vaccination marked the initial onset of petitioner's POTS symptoms. (*Id.*; *see also* Tr. 224-26.)

Accordingly, Dr. Blitshteyn concluded that petitioner's POTS was likely caused by her HPV vaccination.

b. Respondent's Expert, Christopher H. Gibbons, M.D.

Respondent offered an opinion from neurologist and autonomic specialist Dr. Gibbons to defend the claim. Dr. Gibbons is board-certified by the United Counsel of Neurologic Subspecialties in Autonomic Disorders. (Ex. A, p. 1.) He received his medical degree from Albert Einstein College of Medicine in 1999 and his Master of Medical Science degree from Harvard-MIT in 2007. (Ex. B, p. 1.) Dr. Gibbons completed his internship at Yale New Haven Hospital in Greenwich, Connecticut and his neurology residency at Johns Hopkins Hospital in Baltimore, Maryland. (*Id.*) Dr. Gibbons also held a neurophysiology fellowship position at Beth Israel Deaconess Hospital in Boston, Massachusetts ("Beth Israel") from 2003 to 2004. (*Id.*) He currently serves as active staff at Beth Israel and as director of the neuropathy clinic at the Joslin Diabetes Center in Boston. (*Id.*) He has held several teaching positions fat Harvard Medical School since 2004 including instructor in neurology, assistant professor in neurology, and currently serves as an associate professor of neurology. (*Id.*) He has published 62 different pieces of medical literature on neurology and autonomic dysfunction including 45 peer reviewed articles and 17 chapters and reviews. (*Id.* at 4-8.)

With respect to diagnosis, Dr. Gibbons explained that POTS "is characterized by a sustained heart rate increment of 30 beats [per] minute within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension." (Ex. A, p. 2.) He elaborated that "[t]he standing heart rate for all subjects is often 120 beats/minute." (Ex. A, p. 2.) However, he further explained that the general criteria "may not be applicable for individuals with low resting heart rates [and in] individuals aged 12–19 years the required increment is at least 40 beats/minute." (*Id.* (citing Roy Freeman et al., *Consensus Statement on the Definition of Orthostatic Hypotension, Neurally Mediated Syncope and the Postural Tachycardia Syndrome*, 21 CLIN. AUTON. RES. 69 (2011) (Ex. A, Tab 1)).) Dr. Gibbons noted that petitioner was under 19 years old during her autonomic testing and therefore required a heart rate increase of 40 beats per minute ("bpm") to be diagnosed with POTS. (*Id.*) Dr. Gibbons explained that there is only one instance in petitioner's medical records where her heart rate increased by 40 bpm but stressed that "the diagnosis of POTS requires repeated readings to confirm." (*Id.*) Because petitioner's records only document a single reading which would support a diagnosis of POTS, Dr. Gibbons maintained that petitioner most likely did not suffer from POTS. (*Id.*) In response to Dr. Blitshteyn's assertion that POTS may be diagnosed from a single reading, Dr. Gibbons emphasized that a single abnormal reading should only be relied on if it supports the totality of the clinical picture. (Ex. C, p. 1 (citing Freeman et al., *supra*, at Ex. A, Tab 1 (also cited as Ex. C, Tab 1)).) Thus, Dr. Gibbons opined that to accurately diagnose petitioner with POTS, her doctors should have obtained consistent findings or additional clinical evidence supporting such a diagnosis.

Dr. Gibbons also opined that there is no "clear link" between headaches and POTS. (Tr. 392-93.) Although he acknowledged that headaches are a comorbidity of POTS and often seen in POTS patients, he maintained that headaches are common

and should not be considered an indicator of POTS. (*Id.*) He asserted that he would not recommend autonomic testing for a patient based on headaches. (*Id.* at 401.) He further opined that petitioner's pre-vaccination and post-vaccination headaches had no difference in "character" and stressed that there were no significant distinguishable factors such as new onset of headache that awakened her at night or became piercing. (*Id.* at 400, 402-03.) Thus, he concluded that petitioner's post-vaccination headaches were not suggestive of POTS.

Further, Dr. Gibbons explained that petitioner's chronic headache medications, including amitriptyline, trazadone, and Savella, cause both tachycardia and orthostatic symptoms.[8] (Ex. A, p. 2; Tr. 425-26.) Dr. Gibbons concluded that because petitioner's medications are known to cause symptoms of orthostatic tachycardia, they likely affected her autonomic testing results. (Ex. A, p. 2; Tr. 425-26.) In response to Dr. Blitshteyn's contention that petitioner was not taking any medications that could impact her heart rate during her autonomic testing, Dr. Gibbons explained that stopping these medications can also cause tachycardia. He maintained that this does not change his opinion regarding the likelihood that petitioner's medications skewed her autonomic test results. (Ex. A, p. 2 (citing Ex. A, Tab 2; Ex. A, Tab 4).)

In addition to petitioner's chronic medications, Dr. Gibbons contended her deconditioned status at the time of her POTS diagnosis renders the diagnosis unreliable. He discussed several studies showing that deconditioning can cause postural tachycardia and other orthostatic symptoms. (Tr. 451-52; Qi Fu et al., *Cardiac Origins of the Postural Orthostatic Tachycardia Syndrome*, 55(25) JACC 2858 (2010) (Ex. D, Tab 5); Ajay Parsaik et al., *Deconditioning in Patients with Orthostatic Intolerance*, 79 NEUROLOGY 1434 (2012) (Ex. D, Tab 6).) He noted that petitioner's deconditioned status at the time of her testing at the Mayo Clinic is significant in the context of her diagnosis because she showed a 42% decrease in her cardiac testing response compared to her predicted age and sex specific output. (Tr. 450; Ex. 34, p. 29.) Thus, Dr. Gibbons maintained that deconditioning could not be ruled out as a cause for petitioner's orthostatic symptoms.

Given that petitioner's autonomic testing was conducted in a single outpatient vital sign measurement instead of a standardized autonomic test in a controlled laboratory setting, Dr. Gibbons asserted that petitioner's POTS diagnosis is "dubious at

[8] Dr. Gibbons noted that a study conducted to evaluate the effects of Sabella on blood pressure and heart rate in 321 fibromyalgia patients found that following treatment with Savella 50 mg BID for three weeks, "the mean increase in mean 24-hour heart rate from baseline was 13 beats per minute." (Ex. A, p. 2 (citing *Full Prescribing Information, Savella* (herein "Ex. A, Tab 2")).) Additionally, the study revealed that "[i]ncreases in heart rate ≥ 20 beats per minute occurred more frequently in Savella-treated patients when compared to placebo (8% in the Savella 50 mg BID and 100 mg BID treatment arms versus 0.3% in the placebo arm)." (*Id.*) Further, He noted that Trazadone "[m]ay cause orthostatic hypotension and syncope." (*Id.* at 3 (citing *Full Prescribing Information, Oleptro TM* (herein "Ex. A, Tab 3")).) Finally, he noted that the product insert for Amitriptyline states that the medication can cause among other things, "hypertension, myocardial infarction, orthostatic hypotension, palpitations, syncope, [and] tachycardia orthostatic hypotension." (*Id.* (citing *Professional Information Brochure, Elavil ® (Amitriptyline HCl) Tablets and Injection* (herein "Ex. A, Tab 4")).)

best." (Ex. C, p. 2.) He noted that Dr. Fischer's diagnosis was a conclusory statement in an email, stating that it "looks like" petitioner had POTS without any additional discussion of the diagnosis. (*Id.*) Although Dr. Fischer noted that there was resting and symptomatic orthostatic tachycardia, which "can be seen in inappropriate sinus tachycardia with POTS," Dr. Gibbons stressed that "this is not . . . terminology that diagnoses POTS in this patient." (*Id.*) Dr. Gibbons also explained that Dr. Low's diagnosis was made without any discussion of the diagnostic tests he conducted, and that there "is no evidence of autonomic failure on [Dr. Low's] study." (*Id.*) Further, Dr. Gibbons noted that Dr. Kugler diagnosed petitioner with sinus tachycardia following her Holter monitor testing, and not POTS, and that Dr. Fischer's own reporting mentioned that he was not aware of any association between the HPV vaccine and POTS. (*Id.*)

Dr. Gibbons also noted that Dr. Blitshteyn is mistaken to suggest that petitioner's QSART responses support a POTS or SNF diagnosis, specifically because her QSWEAR test results at the Mayo clinic were noted as "normal for all sites." (Ex. C, p. 3; *see also* Tr. 443.) Therefore, Dr. Gibbons concluded that petitioner likely does not suffer from POTS.

In response to Dr. Blitshteyn's hearing testimony about IST, Dr. Gibbons explained that patients with IST have an elevated heart rate without explanation. (Tr. 389-90.) He opined that Dr. Low's language did not constitute a diagnosis of IST; instead, Dr. Gibbons asserted that Dr. Low merely noted that petitioner's autonomic testing results were consistent with what would be "seen in" IST. (*Id.* at 443-44.) Dr. Gibbons also contended that Dr. Low was not petitioner's treating physician and therefore likely did not know that petitioner was taking Savella at the time of the autonomic testing, which could have skewed the results. (*Id.*)

With respect to Dr. Blitshteyn's assertion that petitioner's condition was autoimmune in nature, Dr. Gibbons explained that although it is "not the general experience among the experts in the field" there is continuing research on whether POTS may be caused by an autoimmune reaction. (Ex. A, p. 4 (citing Paola Sandroni et al., *Postural Tachycardia Syndrome: Clinical Features and Follow-up Study*, 74 MAYO CLIN. PROC. 1106 (1999) (Ex. A, Tab 6); Vidya Raj et al., *Psychiatric Profile and Attention Deficits in Postural Tachycardia Syndrome*, 80 J. NEUROL. NEUROSURG. PSYCHIATRY 339 (2009) (Ex. A, Tab 7); Christopher H. Gibbons et al., *Structural and Functional Small Fiber Abnormalities in the Neuropathic Postural Tachycardia Syndrome*, 8(12) PLOS ONE e84716 (2013) (EX. A, Tab 8); Hongliang Li et al., *Autoimmune Basis for Postural Tachycardia Syndrome*, 3 J. AM. HEART ASSOC. e000755 (2014) (ECF No. 85-9)).) While Dr. Blitshteyn noted that antibodies to the ganglionic acetylcholine receptor, ANA, antiphospholipid antibodies, elevated tissue transglutaminase and other autoimmune disorders are associated with POTS, Dr. Gibbons pointed out that all of petitioner's antibody tests were negative and showed no evidence of autoimmune dysfunction. (*Id.*; *see also* Ex. C, p. 3; Tr. 462 (noting that petitioner tested negative for autoantibody titers implicated in autoimmune autonomic ganglionopathy).)

Although Dr. Blitshteyn identified several antibodies which may be relevant to POTS and are not available for testing in the United States, Dr. Gibbons maintained that this claim is "purely speculative." (Ex. A, p. 4 (citing Steven Vernino et al., *Autoantibodies to Ganglionic Acetylcholine Receptors in Autoimmune Autonomic Neuropathies*, 343(12) NEW ENG. J. MED. 847 (2000) (ECF No. 85-10);[9] Christopher H. Gibbons, Steven A. Vernino & Roy Freeman, *Combined Immunomodulatory Therapy in Autoimmune Autonomic Ganglionopathy*, 65 ARCH. NEUROL. 213 (2008) (Ex. A, Tab 11)).) He elaborated that "antibodies should demonstrate pathogenicity, be specific for the disease, active immunization should replicate the disease, passive transfer of antibodies should result in disease and there should be a clinical relationship to antibody reduction." (Ex. C, p. 3.) Because the antibodies referenced by Dr. Blitshteyn have yet to demonstrate these requirements for clinical relevance, Dr. Gibbons opined that they should have no bearing on the current case. (*Id.* (citing Steven Vernino & Vanda A. Lennon, *Neuronal Ganglionic Acetylcholine Receptor Autoimmunity*, 988 ANN. N.Y. ACAD. SCI. 211 (2003) (Ex. C, Tab 6); Steven Vernino et al., *Characterization of Ganglionic Acetylcholine Receptor Autoantibodies,* 197 J. NEUROIMMUNOL. 63 (2008) (Ex. C, Tab 7); Steven Vernino, Steve Hopkins & Zhengbei Wang, *Autonomic Ganglia, Acetylcholine Receptor Antibodies, and Autoimmune Ganglionopathy*, 146 AUTONOMIC NEUROSCI. BASIC & CLIN. 3 (2009) (Ex. C, Tab 8); Zhengbei Wang et al., *Autoimmune Autonomic Ganglionopathy: IgG Effects on Ganglionic Acetylcholine Receptor Current,* 68 NEUROL. 1917 (2007) (Ex. C, Tab 9); Christopher H. Gibbons, Steven A. Vernino & Roy Freeman, *Combined Immunomodulatory Therapy in Autoimmune Autonomic Ganglionopathy*, 65 ARCH. NEUROL. 213 (2008) (Ex. C, Tab 10); Christopher H. Gibbons & Roy Freeman, *Antibody Titers Predict Clinical Features of Autoimmune Autonomic Ganglionopathy,* 146 AUTONOMIC NEUROSCI. BASIC & CLIN. 8 (2009) (Ex. C, Tab 11)).) Thus, Dr. Gibbons concludes that "[t]here is no evidence of autoimmunity in this case, despite extensive testing, including the Mayo [Clinic] paraneoplastic panel." (Ex. A, p. 4.)

Dr. Gibbons further examined how an autoimmune autonomic neuropathy would present, if petitioner's condition was in fact caused by such mechanism. Dr. Gibbons explained that when autoimmune autonomic neuropathy develops following a trigger where molecular mimicry causes damage to the autonomic nervous system, "there will be an antibody mediated response that occurs in an acute to subacute time frame (weeks to a few months)." (Ex. A, p. 4.) An antibody will target the autonomic nervous system and cause autonomic or small fiber dysfunction in a length dependent or ganglionic fashion, resulting in evidence of either small fiber or autonomic neuropathy causing postural tachycardia or diffuse autonomic dysfunction. (*Id.* (citing Gibbons et al., *supra*, at Ex. A, Tab 8); Wolfgang Singer et al., *Prospective Evaluation of Somatic and Autonomic Small Fibers in Selected Autonomic Neuropathies*, 62 NEUROL. 612 (2004) (Ex. A, Tab 12)).) Dr. Gibbons explains that "[i]n any case, there should be evidence of an autonomic neuropathy," which was not seen in this case. (*Id.*) He noted that petitioner's autonomic function testing was normal, aside from her QSART testing

[9] Although this article is reference number 10 in Dr. Gibbons' report, it is bates stamped as Ex. A, Tab 9. Because there are two pieces of literature bates stamped as Ex. A, Tab 9, both will be referenced by their ECF number in this decision.

at the forearm which is "very common in women," and importantly, petitioner's QSART testing was normal in her lower extremities which is inconsistent with small fiber neuropathy. (*Id.*) Further, it is likely that petitioner's QSART responses would be reduced due to her taking Savella at the time of testing. (*Id.*) Consequently, Dr. Gibbons concludes that petitioner's case "does not seem to fit either the temporal or clinical picture consistent with an autoimmune cause of a problem." (*Id.*)

Regarding whether the HPV vaccine can cause POTS, Dr. Gibbons noted that while Dr. Blitshteyn opined that POTS has been associated with viral illness, surgery, pregnancy, trauma, or vaccination, "[n]one of these 'associations' have been linked to the causation of POTS, they are simply temporal associations that have been noted." (Ex. A, p. 3.) Dr. Gibbons objected to Dr. Blitshteyn's use of the word 'trigger' given that "there is no credible or reliable evidence of any known 'trigger' for POTS (Defined as [causing] event to happen or exist)." (*Id.*) Dr. Gibbons explained that retrospective studies such as those cited in Dr. Blitshteyn's report commonly link events with other problems due to temporal proximity and not causal associations. (*Id.*) In a Mayo Clinic report, 27.6% of POTS patients reported a viral illness in the three months preceding their symptoms. (*Id.* (citing Mark J. Thieben et al., *Postural Orthostatic Tachycardia Syndrome: The Mayo Clinic Experience*, 82 MAYO CLIN. PROC. 308 (2007) (Ex. A, Tab 5)).) According to Dr. Gibbons, "[g]iven that nearly 100% of the population will experience at least 1 or more viral illness per year, an associated viral illness would be expected in at least 25% of cases, and likely to be far more based on simple estimates of viral illness in the population." (*Id.*)

Furthermore, Dr. Gibbons noted that Dr. Blitshteyn reported only six cases of HPV vaccine associated POTS out of over 500,000 in the United States. (Ex. A, pp. 4-5.) Dr. Gibbons maintained that this small number of cases suggests "that the HPV vaccine actually protects against POTS because there should be far more case reports by random chance alone," because young women are often diagnosed with POTS and frequently receive the HPV vaccine. (*Id.* at 5.) Thus, Dr. Gibbons explained that "[t]here is no credible evidence that [the HPV vaccine] can cause POTS, only conjecture." (*Id.*)

To support his assertion that there is no evidence that the HPV vaccine can cause POTS, Dr. Gibbons cited a review of medical literature that found no evidence of causality. (Ex. C, p. 2 (citing Breann Butts et al., *Human Papillomavirus Vaccine and Postural Orthostatic Tachycardia Syndrome: A Review of Current Literature*, 32(11) J. CHILD NEUROL. 956 (2017) (Ex. C, Tab 3)).) Additionally, he cited a review of the relationship between HPV vaccines and the development of POTS or CRPS by the European Medical Agency which found "no increased incidence in POTS or CRPS in individuals that have received the vaccine compared to the general population, in over 80 million individuals now vaccinated worldwide. (*Id.* at 4 (citing European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC), *Review Under Article 20 of Regulation (EC) No 726/2004 Human Papillomavirus (HPV) Vaccines* (2015) (Ex. C, Tab 13)).) Dr. Gibbons explained that "available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years

may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year." (*Id.*) He noted that the European Medical Agency "found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting." (*Id.*) Thus, Dr. Gibbons concluded that "[t]here is no scientific evidence at this time that demonstrates by a preponderance of the evidence a causal connection between the HPV vaccine and POTS." (*Id.*)

Moreover, Dr. Gibbons identified deconditioning as a cause POTS. (Tr. 451-52.) He offered medical literature in support of this contention. (Fu et al., *supra*, at Ex. D, Tab 5; Parsaik et al., *supra*, at Ex. D, Tab 6.). A study by Fu et al. sought to determine whether POTS is "attributable to a small heart coupled with reduced blood volume (i.e., deconditioning) and [whether] exercise training could improve or even cure this syndrome." (Fu et al., *supra*, at Ex. D, Tab 5, p. 2859.) The study found:

> 1) cardiac size and mass and blood volume were much smaller in POTS patients compared with healthy sedentary controls; 2) HR was greater, whereas stroke volume was smaller, in patients than in controls during upright posture; 3) the function of the autonomic nervous system was intact in POTS patients; and 4) exercise training increased cardiac size and mass, expanded blood volume, and thus improved or even cured POTS syndrome.

(*Id.* at 2863.) Based on these results, the Fu et al. authors concluded that POTS "per se is indeed a consequence of deconditioning (i.e., specifically cardiac atrophy and hypovolemia)[.]" (*Id.*) Another study by Parsaik et al. examined 184 patients, 84 with POTS and 100 without orthostatic tachycardia. (Parsaik et al., *supra*, at Ex. D, Tab 6, p. 1436.). Of the subjects, 93% had evidence of cardiovascular deconditioning (reduced maximum oxygen uptake during exercise). (*Id.* at 1437.) The study's authors concluded that "[t]he prevalence of deconditioning was very high in patients with disorders of reduced orthostatic intolerance with or without orthostatic tachycardia." (*Id.* at 1438.)

Dr. Gibbons also contended that petitioner's medical history and timing of onset fails to support Dr. Blitshteyn's theory that the HPV vaccine caused her condition. He explained that in petitioner's case, she was noted to have a resting tachycardia as far back as 2008, and headaches beginning at age 7. (Ex. A, p. 3.) He noted that petitioner's heart rate "did not appear to change significantly after the Gardasil vaccine, still continuing to fluctuate in the 90-111 beat per minute range at rest." (*Id.*) Further, petitioner was not suspected of suffering from POTS until nearly one year after her HPV vaccination. (*Id.*) Dr. Gibbons concluded that based on petitioner's medical history and post-vaccination presentation, "there is no medical evidence from which one can reasonably infer a causal relation between the Gardasil vaccination, which was administered 10 months earlier, and the onset of [petitioner's] alleged POTS." (*Id.*) Dr. Gibbons also noted that in each case report cited by Dr. Blitshteyn, the patient's symptoms presented within one month of their vaccination, while petitioner's symptoms

only appeared after ten months, suggesting that Dr. Blitshteyn's case reports fail to support petitioner's theory of causation. (*Id.*)

Thus, because the lack of any evidence of an autoimmune etiology, absence of evidence of a causal relationship between the HPV vaccine and POTS, and the fact that petitioner's clinical presentation is inconsistent with Dr. Blitshteyn's theory of causation, Dr. Gibbons concluded that it is unlikely that petitioner's condition is related to her HPV vaccination.

V. Findings of Fact Regarding Diagnosis and Onset

Before reaching the *Althen* test for causation-in-fact, it is appropriate to first resolve two factual questions that will inform that analysis. First, respondent disputes that petitioner has preponderantly demonstrated that she suffers POTS. Second, if petitioner did have POTS, the parties differ on when POTS first manifested. (ECF No. 118, pp. 61-62; ECF No. 124, pp. 17-18.)

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. § 300aa-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." § 300aa-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). Petitioner must prove by a preponderance of the evidence the factual circumstances surrounding his claim. § 300aa-13(a)(1)(A).

In general, contemporaneous medical records "warrant consideration as trustworthy evidence." *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (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), *aff'd*, 968 F.2d 1226 (Fed. Cir. 1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1948) ("It has generally been held that oral testimony which is in conflict with

contemporaneous documents is entitled to little evidentiary weight.")), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992).

Nonetheless, treating physicians' opinions do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* § 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 Fed. 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), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

Additionally, 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). When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (*citing Blutstein v. Sec'y of Health & Human Servs.*, No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

a. Diagnosis

"The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the [petitioner]'s injury.'" *Andreu v. Sec'y of Health & Human Servs*., 569 F.3d 1367, 1382 (Fed. Cir. 2009) (quoting *Knudsen*, 35 F.3d at 549). "Although the Vaccine Act

does not require absolute precision, it does require the petitioner to establish an injury – the Act specifically creates a claim for compensation for 'vaccine-related injury or death.'" *Stillwell v. Sec'y of Health & Human Servs*., 118 Fed. Cl. 47, 56 (2014) (quoting 42.U.S.C. § 300aa-11(c)). Accordingly, the Federal Circuit has concluded that it is "appropriate for the special master to first determine what injury, if any, [is] supported by the evidence presented in the record before applying the *Althen* test to determine causation." *Lombardi v. Sec'y of Health & Human Servs*., 656 F.3d 1343, 1353 (Fed. Cir. 2011); *see also Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010).

According to Dr. Blitshteyn, there are three diagnostic criteria for POTS: (1) the presence of postural tachycardia on a tilt-table or stand test; (2) a drop in blood pressure or orthostatic hypotension when standing; and (3) the presence of orthostatic intolerance symptoms for at least three to six months. (Tr. 64, 117; *see also* Ex. 44, p. 3.) Dr. Blitshteyn opined that petitioner suffered from POTS based on petitioner's autonomic testing, including her abnormal tilt-table test and ten-minute stand test. (Tr. 117-19; Ex. 22, p. 9; Ex. 34, p. 54.) In addition to petitioner's autonomic testing, Dr. Blitshteyn based her diagnostic opinion on petitioner's symptoms of headache, difficulty concentrating, tachycardia, palpitations, and inability to participate in athletic activities. (Ex. 44, p. 3; Tr. 110-11, 114-19.) Further to this, Dr. Blitshteyn found it especially significant that Drs. Fischer and Low, POTS specialists from the Mayo Clinic, confirmed petitioner's diagnosis. (Ex. 46, p. 2; Tr. 49, 93, 117; *see also* Ex. 34, pp. 36, 53.) Both Dr. Blitshteyn and Dr. Gibbons acknowledged Drs. Fischer and Low to be reputable autonomic clinicians. (Tr. 49, 93, 117 (Dr. Blitshteyn); *id.* at 439 (Dr. Gibbons acknowledging Dr. Fischer to be "quite familiar with autonomic disorders").) Moreover, Dr. Gibbons does acknowledge that petitioner "absolutely" displayed symptoms of orthostatic intolerance. (Tr. 438.) Further, asked whether petitioner had developed symptoms that could reasonably be attributed to POTS, he responded "So certainly, I think, Dr. Fischer at Mayo gave a very clear history and description, and so I think at the Mayo Clinic evaluation, then we do see some nice notation about what might be expected in somebody with symptoms of POTS. Absolutely." (Tr. 422.)

Nonetheless, Dr. Gibbons raised some important caveats regarding the limitations of petitioner's autonomic testing. Specifically, Dr. Gibbons explained that petitioner's chronic headache medications, including Savella, can cause both tachycardia and orthostatic symptoms and in his opinion likely skewed her results. (Ex. A, p. 2; Tr. 425-26.) Dr. Blitshteyn likewise acknowledged that petitioner was taking Savella at the time of her autonomic testing at the Mayo Clinic and that Savella can increase heart rate both supine and standing. (Tr. 120-21.) However, she also noted that had Dr. Low or Dr. Fischer thought that petitioner's use of Savella was a factor in her autonomic testing results, they would have so indicated. (Tr. 121-22.) The Mayo Clinic records confirm Savella was reported as among petitioner's current medications at the time of her autonomic testing, meaning that Dr. Fischer was aware of this fact. (Ex. 34, p. 39.) Moreover, by respondent's own assessment of the complete medical records, petitioner did not experience a consistently elevated heart rate until about July of 2015. (ECF No. 124, p. 12.) This does not correlate to the time when she began

taking Savella, which was in April of 2014. (ECF No. 7-9, p. 8.) This, especially coupled with Dr. Fischer's acceptance of the test results, would cast doubt on the idea that the Savella is the best explanation for the findings of petitioner's autonomic testing.

Additionally, Dr. Gibbons opined that petitioner did not satisfy a POTS diagnosis because the results of the tilt table test fell 2 bpm short of the 40 bpm standard for POTS. (Tr. 447-48, 453.) In contrast, Dr. Blitshteyn maintained that petitioner's standing test, which revealed a heart rate elevation from 90 bpm supine to 130 bpm standing, satisfies the requirements for a POTS diagnosis. She further emphasized that "there is no diagnostic criteria that requires a patient to have consistently present postural tachycardia by precisely 40 bpm every time the patient has a bedside vital signs measurement." (Ex. 46, p. 1.) Although Dr. Gibbons asserted that a 40 bpm elevation in heart rate must be observed on multiple occasions, he conceded that "Dr. Blitshteyn is correct in noting that the [consensus] statement does not define frequency of testing needed to make the [POTS] diagnosis." (Ex. C, p. 2-3). He also acknowledged that a single test result can be diagnostic when supported by the overall clinical picture. (*See* Ex. C, p. 1.) Additionally, petitioner pointed out that petitioner's tilt table testing reflected a heart rate increase of 38 bpm, "a differential exceedingly close to the standard [Dr. Gibbons] insists upon." (ECF No. 118, p. 45.) In light of petitioner's abnormal stand test demonstrating a 40 bpm heart rate increase, petitioner's tilt-table test falling 2 bpm short of the 40 bpm standard is less significant than it otherwise may have been. In particular, Dr. Fischer as the treating physician indicated to petitioner that upon review of the tilt table result that petitioner's heart "sped up LOTS more during the tilting" and concluded that "it looks like you do have POTS." (Ex. 34, p. 36.) Taking both the stand test and tilt-table test together, petitioner's autonomic testing appears to demonstrate an abnormality.

The points raised by Dr. Gibbons do cast some doubt on the reliability of petitioner's POTS diagnosis. Contrary to Dr. Blitshteyn's and petitioner's assertion, the accuracy of that diagnosis is far from "irrefutable." (Tr. 116; Ex. 46, p. 2.) However, given petitioner's abnormal autonomic testing, the presence of orthostatic symptoms, and the fact that two treating autonomic specialists confirmed petitioner's POTS diagnosis, I find that petitioner has preponderantly established that she suffered from POTS at the time of her diagnosis.

b. Onset

The remaining factual question is when petitioner's POTS first manifested. Considering the record as a whole, the onset of petitioner's symptoms of orthostatic intolerance are the best indicator of onset for this condition. Orthostatic symptoms are key to a POTS diagnosis. Both Dr. Blitshteyn and Dr. Gibbons agree that the presence of orthostatic symptoms are required for a POTS diagnosis. (Tr. 218, 220 (Dr. Blitshteyn noting that orthostatic symptoms are required for a POTS diagnosis and conceding that headaches alone do not suggest a POTS diagnosis); *id.* at 392 (Dr. Gibbons testifying that the presence of orthostatic symptoms is required for a POTS diagnosis).)

The diagnosing medical records indicate that petitioner's orthostatic symptoms began six months to a year prior to her visit to the Mayo Clinic on July 2, 2015, which would place the first manifestation of orthostatic symptoms between July 2014 and January 2015. (Ex. 34, p. 37 ("For the past six months or year [petitioner] has gotten dizzy when she stands up and loses vision."). However, petitioner testified that she first began experiencing orthostatic symptoms earlier than that, in the spring of 2013. (Tr. 44.) Her contemporaneous cardiology records can help to further refine this timeframe. Specifically, petitioner reported to her cardiologist on May 15, 2013, that she "has not had any dizziness or syncope at any time." (Ex. 31, p. 120.) Thus, it is most likely that petitioner developed symptoms of orthostatic intolerance sometime between late May of 2013 and July of 2014, which is a minimum of ten months post vaccination.

However, Dr. Blitshteyn opines that onset of petitioner's POTS was earlier based on two factors – (1) the suggestion that petitioner began experiencing headaches two weeks post-vaccination as the first manifestation of her POTS, and (2) the suggestion that there is circumstantial evidence to suggest that petitioner suffered IST long before any tachycardia was first detected. However, neither of these suggestions is preponderantly established on this record for the reasons discussed below. Therefore, the evidence preponderates in favor of onset of petitioner's POTS occurring no earlier than about ten months post-vaccination.

i. Petitioner's Headaches

Petitioner has a documented history of frequent headaches dating back to her childhood.[10] (Ex. 21, p. 26, 32.) However, the parties dispute whether petitioner's pre-vaccination headaches are distinguishable from her post-vaccination headaches. (*See* ECF No. 118, p. 11; ECF No. 124, pp. 3-5.) Petitioner testified that her pre-vaccination headaches "were located on the front of [her] forehead," while her post-vaccination headaches were "located on the top of [her] head." (Tr. 17.) Dr. Blitshteyn also opined that petitioner's pre-vaccination headaches were secondary to allergy attacks, sinusitis, and tonsillitis, and suggested that her post-vaccination headaches were more severe and caused petitioner to miss school and quit athletics. (Ex. 44, pp. 3-4.) She also noted that petitioner consistently reported that her severe headaches began in July 2012 during her post-vaccination medical visits. (Ex. 46, p. 3 (citing Ex. 10, p. 26 (petitioner reporting that her daily headaches began in July 2012).) Thus, Dr. Blitshteyn maintained that petitioner experienced a distinct onset of debilitating headaches two weeks post-vaccination. (Tr. 249.) Conversely, Dr. Gibbons contended that petitioner's pre-vaccination and post-vaccination headaches had no difference in character. (*Id.* at 400, 402-03.)

[10] Petitioner denies having a pattern of headaches beginning at age seven and argues her headaches began in middle school (ECF No. 118, p. 30, 42 n.69; Tr. 12); however, respondent cites to a medical record documenting "frequent headaches in the morning" during a kindergarten physical on July 31, 2007, when petitioner was five years old. (ECF No. 124, p. 1 (citing Ex. 21, p. 32).)

Notwithstanding that petitioner testified to some differences in the location of her headaches, the record evidence does not support the idea that there was a distinct onset of new headaches two weeks after her vaccination. In contrast to her testimony, the medical records show that petitioner's headaches were consistently described as occurring frontally even post-vaccination. On July 19, 2012, when petitioner received her third Gardasil vaccination, she reported experiencing a "frontal" headache for one week. (Ex. 10, p. 28.) Following her third HPV vaccination, on October 9, 2012, petitioner described her headache as "across her for[e]head." (*Id.* at 26.) She later described her headaches as occurring "across her for[e]head and also in the back of her neck" during a medical visit on March 22, 2013. (*Id.* at 19.) Thereafter, petitioner continued to report frontal headaches at various medical visits.[11]

Additionally, when petitioner sought treatment from headache specialist Dr. Whyte for the headaches she now alleges to have been a post-vaccination symptom, the history she reported was that "[s]he started getting headaches around age 7. There has been a steady increase in frequency over the years. A severe headache is described as squeezing with a unilateral frontal location." (Ex. 31, p. 135.) Thus, petitioner did not distinguish the nature of her headaches when seeking treatment. Moreover, while petitioner stressed in her testimony that her childhood headaches had not interfered with her activities (Tr. 12-13), it is also the case that they were concerning enough to be brought to medical attention on multiple occasions. In any event, to the extent many of petitioner's medical records nonetheless identify July 2012 as a starting point for either an increased frequency and/or severity of headaches, the medical records establish that onset of this headache pattern occurred prior to her receipt of the vaccination at issue. As noted above, petitioner was already reporting a one-week history of frontal headaches at the time her July 19, 2012, HPV vaccine was administered. (Ex. 10, p. 28.)

Moreover, even if petitioner's later headaches were not related to her childhood headaches, Dr. Blitshteyn acknowledged that headache or migraine is only a comorbidity among POTS patients. (Tr. 64.) A comorbidity is not the same thing as a symptom. A comorbidity "pertain[s] to a disease or other pathologic process that occurs simultaneously with another." (*Comorbid*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=10685 (last accessed Jan. 13, 2023).) Thus, even if headaches frequently occur as a comorbidity among POTS patients, the headaches are by definition not themselves evidence of the POTS. Additionally, Dr. Gibbons persuasively explained that headache disorders are very common in adolescents and should not be viewed as an indicator of POTS. (Tr. 392-93.) Both Dr. Blitshteyn and Dr. Gibbons indicated that they would not refer a patient for

[11] *See*, *e.g.*, Ex. 31, p. 125 (reporting to Dr. Nelson that her headaches were "frontal/vertex and predominantly right-sided" during a visit on April 10, 2013); *id.* at 75 (describing her headaches as beginning "on the right side of her head in the frontotemporal area" during her visit to the emergency department on April 30, 2013); Ex. 2, p. 3 (informing Dr. Allen that her headache pain "is usually located on the front right side of her frontal cortex, and the pain will occasionally radiate to the back of her head" on May 29, 2013); Ex. 31, p. 135 (reporting to Dr. Whyte that her headaches occurred in a "unilateral frontal location" on July 22, 2013); Ex. 22, p. 1 (reporting that her headache pain "is in the right temporal area but can radiate across the forehead" during her visit to the Mayo Clinic in July 2015).

autonomic testing or suspect POTS based on headaches. (*See id.* at 220, 401.) Further still, when petitioner was diagnosed with POTS, she was *also* diagnosed with migraines, meaning that the diagnosing physicians did not conclude the headaches were a manifestation of POTS. (Ex. 34, p. 23 (Dr. Fischer concluding that petitioner's headaches were "consistent with migraine").) Petitioner also had MRI evidence of a variant consistent with a migraine disorder. (Ex. 33, pp. 24-25; Ex. 22, p. 4 (Dr. Bodensteiner interpreting petitioner's MRI findings of hyperintensity in the frontal lobe representing perivascular spaces as consistent with migraines).)

Thus, in light of all of these considerations, Dr. Blitshteyn is not persuasive in suggesting that the initial onset of petitioner's POTS can be evidenced via her history of headaches.

ii. Undetected Tachycardia

Noting that Dr. Low included IST in his POTS diagnosis (Ex. 34, p. 53), Dr. Blitshteyn links that finding back to the earlier detection of tachycardia in April of 2013.[12] (Tr. 91-92.) Further to this, Dr. Blitshteyn also opined that, although petitioner's tachycardia was first detected during her hospitalization from April 30, 2013, to May 2, 2013 (Ex. 31, p. 76), it likely began much earlier and went undetected. (Ex. 46, p. 4.) Thus, petitioner claims that her "long-running tachycardia likely began soon after her Gardasil vaccination of July 19, 2012." (ECF No. 118, p. 5.) Dr. Blitshteyn explained that petitioner's tachycardia "was only revealed incidentally via a hospitalization for headache in May of 2013, which prompted a visit to Dr. Weiland on May 6, 2013." (Ex. 46, p. 4.) She noted that "it is quite common for teens with POTS to present with headaches or nausea or fatigue and be unaware of their heart rate or blood pressure." (*Id.*)

Even granting Dr. Blitshteyn's first premise that the April 2013 tachycardia finding can be linked to the later POTS diagnosis, the latter part of her reasoning, that it should be assumed the April 2013 tachycardia was itself longstanding, is untenable. Even if it is not unusual for tachycardia to go unnoticed among POTS patients, Dr. Blitshteyn's assertion of an *undetected* tachycardia is still by its very nature inherently speculative. The fact that the tachycardia was an incidental finding does not suggest otherwise. Based on Dr. Blitshteyn's assessment, petitioner argues that her diminution in activity and increase in fatigue beginning in August or September 2012 is evidence of tachycardia.[13] (ECF No. 118, p. 61 (citing Tr. 18).) However, the medical records reflect that between petitioner's vaccination in July 2012 and May 2013, she sought treatment only for complaints of headache and fatigue. (*See*, *e.g.*, Ex. 10, p. 28; Ex. 31, pp. 75, 125, 135; Ex. 2, p. 3 (reflecting headache as petitioner's chief complaint).)

[12] With regard to the question of whether IST could be separately addressed as a distinct diagnosis, see *supra* note 7.

[13] Dr. Blitshteyn testified that petitioner's "inability to participate in her previous activities, like sports, marching band, [and] school work" and her decreased is evidence of undetected tachycardia. (Tr. 96-97.) Dr. Blitshteyn also noted that POTS often goes unrecognized by physicians. (*Id.* at 219.)

Without more, petitioner's complaints of headache, fatigue, and quitting athletic activities, are too vague to constitute evidence of undetected tachycardia. And, in any event, in both her medical encounters and her testimony, petitioner attributed her diminution in activity to her headaches, which are not likely related to her alleged autonomic disorder for the reasons discussed above.[14] (*See*, *e.g.*, Ex. 31, p. 75; Tr. 17-18, 29.)

Indeed, continuing to assume *arguendo* that the April 2013 results indicated the first detection of autonomic or POTS-related tachycardia, there are also some competing reasons to suggest that April 2013 would be a more likely time for petitioner's tachycardia to have started. First, this would roughly correlate to what petitioner testified was the beginning of her orthostatic symptoms that eventually led to her POTS diagnosis, which she placed in the spring of 2013. (Tr. 44.) While the relationship between tachycardia and vague symptoms of fatigue and diminution in activity are tenuous, the potential relationship between petitioner's tachycardia and her orthostatic symptoms would be stronger. (*See* Ex. 34, p. 53 (Dr. Low identifying IST *in the context of POTS*); *see also* Tr. 392 (Dr. Gibbons noting that a POTS diagnosis requires the presence of tachycardia accompanied by orthostatic symptoms such as lightheadedness, dizziness, and shortness of breath); Tr. 431 (Dr. Gibbons stating that reports of tiredness and fatigue are "not diagnostic for POTS"). Additionally, when it was measured earlier, within a month prior, petitioner's heart rate had been observed to be normal. During a physical examination on March 22, 2013, Dr. Weiland recorded that petitioner had "[n]ormal rate, [r]egular rhythm, [n]o murmur." (Ex. 10, p. 20.) While this isolated finding is not definitive, it does cast at least some suspicion the notion that the best assumption is that the tachycardia detected in April 2013 was longstanding. Indeed, while Dr. Gibbons had suggested petitioner may have had a much earlier history of tachycardia (Ex. A, p. 4; Ex. C, pp. 2-3), Dr. Blitshteyn specifically refuted that point (Ex. 46, p. 3). Thus, it should be stressed that, even accepting the earliest detection of tachycardia as related to petitioner's POTS, petitioner's *detected* tachycardia does not suggest any meaningfully earlier onset.

Furthermore, Dr. Gibbons explained that there is a relationship between deconditioning and symptoms of orthostatic intolerance, including tachycardia. (Tr. 451-52; *see*, *e.g.*, Ex. D, Tab 5, p. 1 (citing numerous prior studies regarding deconditioning and POTS-like presentations and suggesting that "[b]ased on these observations, we speculated that POTS per se may be a consequence or signature of deconditioning, namely, cardiac atrophy and hypovolemia.") In fact, notwithstanding that deconditioning is exclusionary under the diagnostic criteria, Dr. Gibbons indicated that deconditioning can itself cause POTS. (Tr. 451.) Thus, even with the hindsight benefit of knowing petitioner was diagnosed with POTS, it is still far from clear that petitioner's inactivity and fatigue are best understood as evidence of ongoing, longstanding tachycardia rather than preceding contributors to later manifesting tachycardia and POTS. In particular, this issue was raised by Dr. Fischer in the context of petitioner's own POTS diagnosis. He indicated that "I actually suspect [petitioner] might have postural

[14] While petitioner may not be competent to testify as to the medical significance of her symptoms, she is certainly competent to testify as to what prompted her to stop participating in sports and other activities.

orthostatic tachycardia syndrome, but it could be that some of her tachycardia changes are related to debilitation from the chronic pain." (Ex. 34, p. 40.)

Dr. Blitshteyn disputes that deconditioning leads to tachycardia. (Tr. 102.) She acknowledges that sedentary people will experience higher heartrates but disagrees that they will experience a pathologically increased heartrate for years. (*Id.*) However, the notion that this case would involve a years-long pathologically increased heartrate is Dr. Blitshteyn's *assumption* based on her contention that the April/May 2013 findings can be linked to Dr. Low's later July 2015 report to suggest a longstanding IST. However, respondent raises two reasons to doubt this assumption. First, Dr. Gibbons contends there is a separate explanation for the April/May 2013 findings in that petitioner's evolving heartrate activity during that testing is consistent with effects of the amitriptyline and Depakote she was taking at the time. (Tr. 412-16, 519-21.) Second, there is at least some evidence that petitioner's heart rate did not remain consistently elevated after that point. According to respondent, petitioner's heartrate was not demonstrated to be consistently elevated until around the time she was diagnosed with POTS, by which time her medical records began to include specific references to deconditioning. (ECF No. 124, pp. 11-12.) Respondent stresses that petitioner's heartrate was measured within normal limits during a number of encounters occurring between the time of her April 2013 tachycardia and her later POTS diagnosis. (*Id*. (citing Ex. 31, p. 121 (78 bpm on May 15, 2013); Ex. 10, p. 8 (notation of regular rate and rhythm on June 24, 2013); Ex. 31, p. 134 (68 bpm on July 26, 2013); Ex. 33, p. 90 (76 bpm on September 1, 2013); Ex. 31, p. 145 (74 bpm on September 5, 2013); Ex. 31, p. 184 (72 bpm on January 20, 2014); Ex. 3, p. 41 and Ex. 30, p. 12 (89 bpm on April 8, 2014 and 80 bpm on May 23, 2014).) Indeed, in defending the POTS diagnosis itself, Dr. Blitshteyn stressed that POTS patients do not have constant tachycardia. (Ex. 46, p. 1; Tr. 125.) All of this suggests that petitioner's history prior to July of 2015 may be more consistent with POTS alone than it is with "POTS with IST."

Thus, in light of all of these considerations, Dr. Blitshteyn is not persuasive in suggesting that the initial onset of petitioner's POTS can be evidenced based on either *undetected* tachycardia and/or her diminution in activity. Even accepting arguendo that petitioner's first detected tachycardia represented the onset of her condition, this would still place onset around the time of onset of her orthostatic symptoms, *i.e.* just shy of ten months post-vaccination.

VI. Causation Analysis

As explained above, petitioner's burden is to demonstrate by preponderant evidence, each of the three *Althen* prongs used to determine actual causation (i.e., an acceptable medical theory, a logical sequence of cause and effect, and a proximate temporal relationship). *Althen*, 418 F.3d at 1278.

a. *Althen* Prong One

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549. Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon*, 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

In this case, Dr. Blitshteyn's opinion must account for three controverted points in order to be persuasive. First, does POTS as a syndrome have any established underlying cause? Second, if so, is that underlying cause autoimmunity? And third, if POTS can be said to be autoimmune, is vaccination a relevant cause or trigger of that autoimmune process? However, the evidence is shaky with respect to the first two questions and all but absent on the third. Thus, there is not preponderant evidence sufficient to satisfy *Althen* prong one.

First, the etiology for POTS is multifactorial (Tr. 65) and therefore does not necessarily involve autoimmunity (*e.g.*, Ex, 71, p. 6 (a review article filed by petitioner characterizing the autoimmune hypothesis of POTS as "attractive" but "await[ing] verification" and "not the only one, though"). POTS is itself only a syndrome. (*Id.* at 116.) As the experts explained and the literature reflects, POTS may be a final common pathway to explain multiple pathophysiological processes that affect the body's hemodynamics. (*Id.* at 458 (Dr. Gibbons explaining that there are "an array of disorders that can lead to the sort of common syndrome we're talking about").) For example, although POTS has sometimes been shown to follow illness, it has also been associated to trauma and pregnancy. (Ex. 44, p. 3 (citing Thieben et al., *supra*, at Ex. 44-1; Blitshteyn, *supra*, at Ex. 44-2).) Additionally, Dr. Gibbons persuasively explained that deconditioning, though considered a separate entity, can cause POTS. (Tr. 451-52; *see also* Fu et al., *supra*, at Ex. D, Tab 5; Parsaik, *supra*, at Ex. D, Tab 6.)

Importantly, while Dr. Gibbons acknowledged that autoimmune autonomic ganglionopathy is a specific type of autonomic disorder for which autoimmunity is established (Tr. 496, 497-98), petitioner has not demonstrated any basis for concluding that the underlying etiology of that specific, established disorder, can be applied more generally to other autonomic dysfunction.[15] At best, petitioner has established, as Dr. Gibbons acknowledged, that it is plausible, but yet to be established, that POTS more

[15] And, in any event, as described below with regard to *Althen* prong two, petitioner's clinical presentation is not consistent with autoimmune autonomic ganglionopathy.

broadly has any autoimmune basis. (*See id.* at 503.) Thus, both the experts' testimony and the medical literature suggest that substantial questions remain regarding the etiology and cause(s) of POTS generally. Petitioner's theory therefore builds from an uncertain starting premise.

Second, and relatedly, to the extent the potential remains for at least a subset of POTS cases to be autoimmune, the search for any established autoimmune pathway is still preliminary. Petitioner argues that "the scientific community agrees that post-vaccination POTS is rooted in the autoimmune process." (ECF No. 118, p. 49.) In that regard, Dr. Blitshteyn offered several studies that begin to look at the specific antibodies that could be implicated in POTS.[16] However, these studies do not combine to collectively provide strong evidence that POTS is autoimmune given that they purport to implicate *different* possible autoantibodies and explore different possible pathways to autoimmunity. Focusing on the adrenergic receptor antibodies highlighted by Dr. Blitshteyn, one study stressed by petitioner explains that this is a "large family of receptors" and that the strength of associational findings among different adrenergic receptor antibodies has been variable, with some only weakly correlated to symptomology in prior studies. (Isabella Kharraziha et al., *Serum activity against G protein-coupled receptors and severity of orthostatic symptoms in postural orthostatic tachycardia syndrome,* 9 J. AM. HEART ASSOC. 1 (2020) (Ex. 65).) Moreover, while that study found some correlation between certain of this type of antibody and the severity of orthostatic symptoms, the results also indicated that "[s]ome GPCR [G-protein-coupled receptors] activity was seen in all patients with POTS and all controls." (*Id.* at 4.) The Hineno study discussed below, likewise found the antibodies at issue to be present in both subjects and controls but did not find any correlation between these receptor antibodies and the severity of symptoms of purported post-HPV autonomic dysfunction. (Hineno et al., *supra*, at Ex. 50, p. 4 ("There was no significant association between the major symptoms including dysautonomic symptoms and the serum levels of autoantibodies . . . .").) This issue is further addressed in another paper stressed by Dr. Blitshteyn. In 2016, Takahashi et al. published a study in the *Journal of Neuroimmunology*. That study examined 32 patients with chronic central nervous

[16] Thieben et al., *supra*, at Ex. 44-1 (examining ganglionic AChR antibody); Vernino et al., *supra*, at Ex. 44-6 (same); Wang et al., *supra*, at 44-7 (examining autoimmunoreactive IgG); Li et al., *supra*, at Ex. 44-8 (examining α1-adrenergic receptor autoantibodies); Blitshteyn et al., *supra*, at Ex. 44-9 (examining antinuclear antibodies ("ANA"); Dahan et al., *supra*, at Ex. 44-10 (referencing ANA, ganglionic A3 acetylcholine receptor antibodies, as well as "various autoantibodies"); Takahashi et al., *supra*, at Ex. 44-21 (examining CluN2B-BT2, GluN2B-CT, and CluN1-NT antibodies); Fedorowski et al., *supra*, at Ex. 46-6 (examining α1-adrenergic and β1/2-adrenergic receptor autoantibodies); Ruzieh et al., *supra*, at Ex. 46-7 (review paper addressing a number of potentially implicated autoantibodies as discussed in prior papers); Chandler, *supra*, at Ex. 46-9 (mentioning case reports regarding β2-adrenergic and muscarinic-2 receptor autoantibodies); Blitshteyn & Brook, *supra*, at Ex. 46-10 (anti-NMDA receptor antibodies); Hendrickson & Tormey, *supra*, at Ex. 46-11 (citing a patient positive for β2-adrenergic, muscarinic M2, and α adrenergic receptor autoantibodies); Kafaie et al., *supra*, at Ex. 46-12 (case report negative for anti-NMDA antibodies, but positive for adrenergic and muscarinic receptor autoantibodies); Schofield & Hendrickson, *supra*, at Ex. 46-13 (discussing additional autoantibodies in the context of small fiber neuropathy); Hineno et al., *supra*, at Ex. 50 (examining adrenergic antibodies); William T. Gunning III et al., *Inflammatory Biomarkers in Postural Orthostatic Tachycardia Syndrome with Elevated G-Protein-Coupled Receptor Autoantibodies*, 10 J. CLINICAL MED. 623 (2021) (Ex. 64).

system symptoms that presented for care after receiving an HPV vaccine. The study found elevated cytokines as well as GLuN2B-NT2, GluN2b-CT, and GluN1-NT antibodies.[17] (Takahashi et al., *supra,* at Ex. 44-21, p. 1.) The antibodies detected by the Takahshi study are not the same antibodies Dr. Blitshteyn invokes as part of her causal theory. The authors explain that a number of prior studies have implicated a number of different antibodies and that "[t]he presence of various autoantibodies in CSF may explain the diversity of CNS symptoms in patients after HPV vaccination. Further studies are needed to elucidate the relationship between CNS symptoms and autoantibodies." (*Id*. at 7-8.) On the whole, the literature is careful to explain that the exact relationship between POTS and these various autoantibodies is not established.

Nonetheless, Dr. Blitshteyn also asserts that an animal model shows that rabbits immunized with a peptide similar to α-1 adrenergic receptors can produce POTS, lending further support to the hypothesis that adrenergic receptor antibodies are disease-causing. (Tr. 152, 163-64 (citing Ex. 78).) With respect to the Li et al. study, however, Dr. Gibbons emphasized that the study examined only eight rabbits with no control group for comparison. (Tr. 475, 477.) Dr. Gibbons pointed out that rabbits have different physiology from humans as they are quadrupeds and are horizontal most of the time. (*Id.* at 476.) Therefore, Dr. Gibbons asserted that it was uncertain whether the rabbits in the Li et al. study showed signs of POTS. (*Id.*) Dr. Gibbons also discussed the authors' use of multiple antibody targets simultaneously instead of selective antibody targeting, noting that it made it difficult to interpret the findings. (*Id.* at 477.) Further, the authors did not perform autopsies or take tissue samples; therefore, Dr. Gibbons indicated that the authors could not adequately determine the effects of the experiment on the rabbits. (*Id.*) Thus, Dr. Gibbons persuasively explained that the Li et al. study did not establish an autoimmune basis for POTS.

Third, and finally, even if petitioner was able to preponderantly show that at least some cases of POTS should be considered autoimmune, this would not in itself evidence the HPV vaccine as causal. Persuasive evidence linking the HPV vaccine to this suspected autoimmune process is lacking. While Dr. Blitshteyn did at turns invoke molecular mimicry to explain how the HPV vaccine could be causally relevant, this was not fully explained or substantiated. (*See*, *e.g.*, Tr. 153-55, 167-68, 209.) Molecular mimicry "is a generally accepted scientific principle, [but] mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 18, 2019)). Rather, this final

[17] Significantly, the authors explain with respect to the antibody findings that "[o]ur data showed that antibodies to CluN2B-NT2 were elevated at 10-30 months after onset and cognitive disorder became apparent after around 21 months from the first shot of HPV vaccine." (Takahashi et al., *supra,* at Ex. 44-21, p. 7.) However, as discussed with respect to *Althen* prong three below, this is outside of the timeframe that Dr. Blitshteyn identified as enabling a medically reasonable causal inference. (Tr. 217-18.) Thus, even assuming these findings were definitive as markers of autoimmunity, it would still raise a further question of whether these antibodies were, in fact, causal, rather than merely manifestations of the autoimmune process.

culminating aspect of Dr. Blitshteyn's opinion is based primarily upon epidemiologic studies that purport to associate the HPV vaccine to a relevant constellation of autonomic symptoms. I previously addressed this issue in a prior case. *Balasco v. Sec'y of Health & Human Servs.*, No. 17-215, 2020 WL 1240917 (Fed. Cl. Spec. Mstr. Feb. 14, 2020).[18] In that case I addressed this literature using a shorthand label of "HPV-vaccine Syndrome." Looking at the body of literature cited in that case, I concluded that the studies were unpersuasive and largely conclusory in their grouping of purported post-vaccination adverse events. Additionally, many rely on self-reporting. *Id*. at 30-31. Several of the papers discussed in that case have also been filed in this case. Specifically: Blitshteyn, *supra, at* Ex. 44-2; Li et al., *supra*, at Ex. 44-8; Dahan, *supra*, at Ex. 44-10; Kinoshita, *supra*, at Ex. 44-13; Brinth et al., *supra*, at Ex. 44-14; Fedorowski, *supra*, at Ex. 46-6; Ruzieh, *supra*, at Ex. 46-7; Blitshteyn & Brook, *supra*, at Ex. 46-10.

For example, petitioner in this case stresses the Ozawa and Kinoshita papers in her post-hearing brief. (ECF No. 118, p. 27 (citing Exs. 55, 44-13.) I continue to find these studies unpersuasive for the reasons discussed in *Balasco*. Regarding Kinoshita, many of the examined symptoms were experienced by only a minority of the subjects. The Ozawa study was larger and sought to delineate those with more definite or probable presentations, but still had a large population of "undiagnosed" patients with fewer common symptoms. Moreover, the study relied on newly created diagnostic criteria, requiring the authors to acknowledge that the validity and reliability of the criteria were not established. A significant shortcoming that seems to be repeated throughout this body of literature is that the subjects are selected *because* they already appear to fit the hypothesis. Yet, as the Takahashi study authors indirectly suggested in the above-quoted passage, the diversity of clinical presentations coupled with a diversity of suspected autoantibodies must at a minimum raise the question of whether these subjects can reasonably be grouped together, because it is far from clear that they are all experiencing the same autoimmune condition (if, in fact, they are experiencing any autoimmune condition at all). (Takahashi et al., *supra,* at Ex. 44-21, p. 8.)

It is also worth noting that many of these studies – Ozawa, Kinoshita, and Hineno – focus on Japanese adolescents. Thus, the Kinoshita study observed that two prior cohort studies, one in Italy and another in Denmark and Sweden, had not produced similar results, leaving an unresolved question of why Japanese girls in particular are more frequently involved. (Kinoshita et al., *supra,* at Ex. 44-13, p. 15.) In that regard, Dr. Gibbons has also offered a literature review that persuasively discusses the limitations of these types of studies and case reports and further contrasts those findings against other available data. (Ex. C, Tab 3.) He additionally cites a large-scale population study that casts doubt on the plausibility of a post-HPV vaccine autonomic disorder or syndrome. The study, conducted by the European Medical Agency, found

[18] Further, as discussed below, there have been several prior decisions in the Vaccine Program by other special masters addressing and uniformly rejecting causal theories seeking to link the HPV vaccine to POTS and/or autonomic nervous system dysfunction. Of course, none of these prior cases are binding and they do not dictate the outcome in this case.

that of eighty million girls and women who received the HPV vaccine, there was no increased incidence of POTS or CRPS compared to the general population. (PRAC, *supra*, at Ex. C, Tab 13.) Petitioner, of course, stresses that this study is likewise not beyond criticism. (ECF No. 118, p. 10 (citing Peter C. Gøtzsche & Karsten Juhl Jørgensen, *EMA's mishandling of an investigation into suspected serious neurological harms of HPV vaccines,* BMJ EVIDENCE-BASED MED. 1 (2021) (Ex. 60)).) Additionally, epidemiology is generally not well equipped to prove a negative and petitioners are not obligated to epidemiologically prove their cases in this program. Nonetheless, even after review of these criticisms, and without treating the EMA conclusion as dispositive, the scale of the data involved is impressive and does tend to highlight the selection bias evident in many of the other smaller competing studies that begin by collecting small groups of subjects who already suspect a post-vaccine symptomology and thereby declare an association.

Of particular importance in this case, Dr. Blitshteyn identified the Hineno et al. study as key in establishing an autoimmune basis for *post-vaccination* POTS. (*E.g.,* Tr. 127, 153-54, 168.) This is because the Hineno et al. study purports to associate the above-discussed adrenergic antibodies with the HPV vaccine. (Tr. 321; Hineno et al., *supra*, at Ex. 50.) However, Dr. Gibbons identified three main flaws that diminish the utility of the study. (Tr. 478-85.) First, none of the study's subjects were diagnosed with POTS. (*Id.*) Second, the range of antibody titers between control subjects and patients who received the HPV vaccine and exhibited diffuse symptoms were overlapping. (*Id.*) Third, the study did not compare patients who experienced symptoms but did not receive the vaccine. (*Id.*) Thus, Dr. Gibbons concluded that the Hineno et al. study provided no reliable evidence that the HPV vaccine can induce the antibodies at issue and cause POTS. In fact, he claimed the study merely showed that "everybody has these antibodies." (*Id.* at 484.)

Even apart from its other limitations, the Hineno study is especially unpersuasive with respect to implicating the HPV vaccine as causal. According to the authors, "[t]his preliminary study provides evidence that post-vaccination abnormal autoimmunity plays an important role in the development of unique symptoms after HPV vaccine." (Hineno et al., *supra,* at Ex. 50, p. 1.) The study gathered 55 adolescent girls who believed they were suffering post-HPV vaccine symptoms. (*Id.* at 2.) According to the authors, these symptoms were concerning for orthostatic dysregulation. (*Id*. at 3.) The authors further note that prior papers have suggested the possibility that adrenergic and muscarinic receptor antibodies may be associated with such conditions. (*Id*. at 4.) However, the study compared these patients to a single control group of 57 control subjects who were *both* healthy *and* unvaccinated. (*Id*. at 2.) This completely fails to isolate the HPV vaccine as a variable. Without any healthy and vaccinated control group and/or a symptomatic and unvaccinated control group, the study cannot be illuminating as to whether the HPV vaccine was a factor in bringing about the presence of the autoantibodies because the subjects were all brought into the study on the basis that they were experiencing symptoms already (potentially) concerning for these autoantibodies regardless of their vaccination status. Thus, the study is conclusory. Indeed, a passage from the study explicitly concedes this:

> It is well known that autonomic nerve dysfunction including POTS and CRPS do develop in young girls without prior vaccination. Recently, it has been reported that a significant number of non-vaccinated Japanese girls suffer from similar symptoms described as adverse effects after HPV vaccination . . . [i]t is conceivable that low serum levels of these autoantibodies against autonomic nerve receptors can result in the occurrence of orthostatic dysregulation and/or CRPS in nonvaccinated individuals.

(*Id*. at 4-5) (internal citations omitted).

It should be noted that this is *not* a close case. Special masters have repeatedly rejected claims that the HPV vaccine can cause POTS and/or autonomic dysfunction and this case is no different based on my review of this record. As noted above, I previously addressed this type of claim in the *Balasco* case. Additionally, other special masters have reached the same result in a number of other cases. *See*, *e.g.*, *America v. Sec'y of Health & Human Servs.*, No. 17-542V, 2022 WL 278151 (Fed. Cl. Spec. Mstr. Jan. 4, 2022); *E.S. v. Sec'y of Health & Human Servs.*, No. 17-480V, 2020 WL 9076620 (Fed. Cl. Spec. Mstr. Nov. 13, 2020); *Johnson v. Sec'y of Health & Human Servs.*, No. 14-254V, 2018 WL 2051760 (Fed. Cl. Spec. Mstr. Mar. 23, 2018); *Combs v. Sec'y of Health & Human Servs.*, No.14-878V, 2018 WL 1581672 (Fed. Cl. Spec. Mstr. Feb. 15, 2018); *L.A.M. v. Sec'y of Health & Human Servs.*, No. 11-852V, 2017 WL 527576 (Fed. Cl. Spec. Mstr. Jan. 31, 2017); *Turkopolis v. Sec'y of Health & Human Servs*., No. 10-351V, 2014 WL 2872215 (Fed. Cl. Spec. Mstr. May 30, 2014). In fact, the Chief Special Master has gone so far as to caution litigants in the context of attorneys' fees and costs that "counsel are forewarned to take care in litigating HPV cases" and that fees might be denied for future cases that "trod the same ground but without any new and far more reliable scientific or medical evidence to support the claim."[19] *E.S. v. Sec'y of Health & Human Servs*., No. 17-480V, 2021 WL 5816006, at *5 (Fed. Cl. Spec. Mstr. Nov. 10, 2021).

Indeed, in March of 2019, the American Autonomic Society published a "position statement" in *Clinical Autonomic Research*. (Alexandru Barboi, *Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society,* CLIN. AUTONOMIC RES. 1 (2019) (Ex. 51).) The statement indicates that "[a]t this time, the American Autonomic Society finds that there are no data to support a causal relationship between HPV vaccination and CRPS, chronic fatigue, and postural tachycardia syndrome to other forms of dysautonomia." (*Id*. at 1.) The statement further concludes that "[c]ertain conditions are prevalent in the same populations that are vaccinated with the HPV vaccine (peri-pubertal males and

[19] This is only to underscore as a matter of background that this type of case has a relatively extensive, but uniformly unsuccessful, history of litigation in this Program. I do not herein reach the question of whether this petition was brought with a reasonable basis nor is my intent to in any way forecast that analysis.

females). This association, however, is an insufficient proof of causality." (*Id*.) In November of 2019, the same journal published a letter to the editor by Dr. Blitshteyn responding to the March of 2019 position statement. (Ex. D, Tab 10; Svetlana Blitshteyn, *Human papillomavirus (HPV) vaccine safety concerning POTS, CRPS and related conditions,* CLIN. AUTONOMIC RES. 1 (2019) (Ex. 52).) In that letter, Dr. Blitshteyn was critical of several studies the Society had relied upon to *disclaim* any causal link between the HPV vaccine and POTS. Dr. Blitshteyn urged that "the argument for HPV vaccine safety with respect to POTS, CRPS and related conditions [is] largely unsubstantiated." (Blitshteyn, *supra,* at Ex. 52, p. 2.) However, with regard to any affirmative case favoring vaccine causation, she stated that "I appreciate the American Autonomic Society's position statement on HPV vaccines and autonomic disorders and agree with its conclusion that given the existing evidence to date, a causal relationship has not been supported."[20] (*Id*. at 1.) Dr. Blitshteyn confirmed multiple times during the hearing that she stands by this statement. (Tr. 174, 176-77.) Thus, petitioner's own expert testified on direct examination regarding the link between HPV vaccine and POTS that at least as of 2018 "I felt that there isn't, you know, significant evidence in science that there is a causal relationship" and that as of 2018 "it wasn't supported."[21] (Tr. 173.)

[20] Interestingly, Dr. Blitshteyn testified that she wrote this letter with Vaccine Act litigation in mind. (Tr. 171-72.) However, the more equivocal understanding expressed in Dr. Blitshteyn's letter – effectively urging that the question of vaccine causation remains ripe for exploration rather than actually supported – is not an isolated instance. For example, the record of this case includes a 2014 paper in the European Journal of Neurology in which Dr. Blitshteyn presents six case reports of patients who developed POTS after receiving HPV vaccinations. (Ex. 44., Ref. 2.) Dr. Blitshteyn presents this in her first report as an important "first ever" case series supporting her opinion. (Ex. 44, p. 4.) Although there is no question that the article hypothesizes a causal link, Dr. Blitshteyn is careful in that article to couch the link in terms of what is "possible" or what "may occur." (*Id*. at 5.) She explains that "[t]he temporal association between vaccination with Gardasil and the onset of symptoms of POTS in healthy young women is significant and deserves further investigation for assessment of a *possible* causal relationship." (*Id*. at 4 (emphasis added).) Later, in 2016, Dr. Blitshteyn presented a further case report in *Lupus*. In that report, Dr. Blitstheyn hypothesized that the presence of anti-NMDA receptor antibodies and response to immunotherapy suggested that the etiology of the patient's POTS was autoimmune and related to vaccination. (Ex. 46.) However, the report acknowledges that the key question of whether the anti-NMDA receptor antibodies are "coincidental or causative" is unknown. (*Id*. at 2.) Additionally, Dr. Blitshteyn was coauthor on a November 2018 paper in *Immunologic Research* urging that "[b]eing cognizant that a temporal relationship between vaccination and symptom onset does not necessarily equate to causality, mounting evidence of case series calls for well-designed case-control studies to determine the prevalence and possible causation between these symptom clusters and HPV vaccines." (Ex. 62, p. 1.)

[21] During the hearing, Dr. Blitshteyn was asked to address the seeming conflict between what she has stated publicly in her 2019 letter to *Clinical Autonomic Research* and the opinion she has offered in this case. (Tr. 169-175.) She explained that the distinction derives from different degrees of certainty. With respect to her 2019 letter, she indicated that "I agree that we don't have a [*sic*.] causal evidence in scientific terms that HPV vaccines cause POTS. We don't have that." (Tr. 174.) She added that "It's very hard to prove causation in science." (*Id*.) However, with respect to her reports in this case, she also indicated that "I still stand by my opinion." (Tr. 175.) Asked if she was drawing a distinction between the Vaccine Act standard (*i.e*., preponderant evidence under *Althen*) and the scientific causality standard, she responded "absolutely." (*Id*.) As noted above, a petitioner "may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory." *Balasco*, 2020 WL 1240917, at *32 (citing *Andreu*, 569 F.3d at

Petitioner argues that the state of the relevant science has changed since 2018; however, this is not well supported on this record. (ECF No. 118, pp. 24-25.) For example, while Dr. Blitshteyn asserts that the body of evidence has continued to grow since she wrote her 2019 letter, she characterized the status of the question in 2021 at the time of the hearing as "still being debated in science." (Tr. 173.) At one point during the hearing, Dr. Blitshteyn was asked if her opinion was based on case reports alone. (Tr. 137.) She responded, "No. No. We have newer studies that show the possible signal of adverse events in POTS, CRPS. When you review a database, one is a study from Chandler . . . ." (*Id*.) Importantly, however, the Chandler study, which is a part of the record of this case, was specifically discussed within Dr. Blitshteyn's 2019 letter in which she nonetheless agrees the causal link at issue is not established by "existing evidence." (Blitshteyn, *supra,* at Ex. 52, p. 3.) Accordingly, the Chandler study is not in itself evidence that refutes Dr. Blitshteyn's letter statement even if it is evidence that she relies upon in asserting her hypothesis. Most of the papers cited by petitioner in her post-hearing brief as providing either "later" or "newer" support for petitioner's theory predate Dr. Blitshteyn's letter.[22] (ECF No. 118, pp. 24-25.) Rather, Dr. Blitshteyn

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1367). Additionally, Federal Circuit precedent indicates that the Vaccine Program is meant to allow for exploration of new ideas in an area bereft of a perfect understanding of how vaccines affect the body. *See Andreu*, 569 F.3d at 1379 (citing *Althen*, 418 F.3d at 1280, *Capizzano*, 440 F.3d at 1324; *Daubert v. Merrell Dow Pharms, Inc.*, 509 U.S. 579, 593 (1993). Thus, petitioners are in general permitted to rely on circumstantial evidence. *Althen*, 418 F.3d at 1280. Accordingly, the mere fact that Dr. Blitshteyn is drawing a distinction between what has been scientifically proven and what she can reasonably opine in this case is not in itself problematic. However, the Federal Circuit has also "consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Boatmon*, 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

[22] The two reports Dr. Blitshteyn prepared for this case are dated from 2017. (Exs. 44, 46.) However, petitioner subsequently filed additional literature marked as Exhibits 50-78 on May 19, 2021. (ECF No. 106.) Based on my review, nine of those articles have publication dates of 2020 or later. (Exs. 57, 59, 64, 65, 66, 70, 74, 76, and 77.) Of those, three (Exs. 74, 76, 77) address the clinical course and effects of POTS without respect to causation. Two of the studies (Exs. 64-65) address the presence of the antibodies that form the basis of Dr. Blitshteyn's theory, but without reference to the HPV vaccine. Those two studies are addressed above. One article is an abstract only. (Ex. 70.) Had the complete study been filed, it purported to find a genetic risk for autoimmunity among POTS patients. (*Id*.) Exhibit 59 is a 2020 review study that assembled data from 24 prior studies with a total population of about 97,000 subjects. That review found that there was an increased risk of symptoms "associated" with POTS following HPV vaccination, but confirmed that no diagnosed cases of POTS were captured by any of the studies. Exhibit 57 is a 2020 paper that seeks to publicize certain methodological details from HPV vaccine safety trials. Exhibits 59 and 57 speak more to Dr. Blitshteyn's unwillingness, as stated in her letter, to accept that the available evidence rules out a casual relationship than they do to the notion that any substantial new evidence has come along more recently to buttress her own hypothesis. Exhibit 66 is a review paper by Martinez-Lavin and Tejada-Ruiz hypothesizing that a post-HPV vaccine syndrome is comparable to Gulf War Illness and Macrophagic Myofaciitis, thereby evidencing that all are potentially disorders of autoimmune autonomic dysfunction. Although later published, this paper largely deals with data from prior publications from 2019 and earlier. Moreover, the premise of the paper – relying on comparison to Gulf War Illness – is not persuasive. *See, e.g. J.F. v. Sec'y of Health & Human Servs*., No. 13-799V, 2022 WL 5434214, *30 (Fed. Cl. Spec. Mstr. Sept. 9, 2022) (explaining in the context of the ASIA hypothesis that "the starting premise that each of the four originating conditions (MMF, siliconosis, post-vaccination phenomena, and Gulf War Syndrome) have been identified as conditions with well understood causes, or even in some cases as conditions at all, remains controversial."); *Skinner-Smith v.*

indicated that her position is informed at least in part by the fact that she is not convinced by evidence *refuting* a causal relationship. (Tr. 173.) For example, she confirmed in her second report that the type of study she herself considers necessary to resolve the question has not been done. (Ex. 46, p. 6.) However, the fact that a possible causal relationship has not been disproven is not meaningful support where petitioner bears an affirmative burden of proof.

In sum, I do not find preponderant evidence of a reliable medical theory causally connecting petitioner's HPV vaccine to her POTS. At best, petitioner has provided some tentative evidence that it may be plausible that some cases of POTS are autoimmune while entirely failing to establish any reliable link to the HPV vaccine. Accordingly, petitioner has failed to satisfy *Althen* prong one.

b. *Althen* Prong Three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Although a specific time interval for onset of POTS following vaccination has not been established, based on the appropriate timeframe for other neurological disorders, Dr. Blitshteyn offered twelve weeks as the maximum time interval for onset of POTS following vaccination. (Tr. 217-18.) She opined that given the proposed pathological process involving autoimmunity via molecular mimicry, post-vaccination POTS should manifest within three months of vaccination. (*Id.*) Dr. Blitshteyn further clarified that eight months would be too long to establish an appropriate temporal interval between vaccination and onset. (*Id.* at 218.)

In the above fact finding, I concluded that there is not preponderant evidence that petitioner suffered POTS prior to May of 2013, which is ten months after vaccination. Even if one assumed that onset was the first detection of tachycardia, that would place

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Sec'y of Health & Human Servs., No. 14-1212V, 2022 WL 4116896, at *33-34 (Fed. Cl. Spec. Mstr. Aug. 15, 2022) (discussing literature addressing multiple factors under debate as possible causes of Gulf War Syndrome and finding petitioner failed to leverage Gulf War Syndrome to support a medical theory linking Tdap vaccine to chronic fatigue syndrome).

onset in late April 2013, which is still greater than eight months post-vaccination, beyond what Dr. Blitshteyn explicitly confirmed is too remote to infer vaccine causation. As discussed above, Dr. Blitshteyn's rationales for placing onset earlier were not persuasive on this record. Thus, petitioner has not preponderantly established an appropriate temporal interval as required by *Althen* prong three.

c. *Althen* Prong Two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280) (stating that "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'"). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder*, 88 Fed. Cl. at 746 n.67 (stating that "there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

Petitioner has not presented preponderant evidence showing a logical sequence of cause and effect between petitioner's HPV vaccine and her POTS. As an initial matter, the fact that petitioner has failed to satisfy *Althen* prongs one and three necessitates a finding that there is no logical sequence of cause and effect in this case. Additionally, none of petitioner's treating physicians, including those that diagnosed her as having POTS, opined that her condition was vaccine-caused.[23] Dr. Gibbons also persuasively explained that if one were to suppose an autoimmune basis for autonomic dysfunction, one should see manifestation of dysautonomia beyond the POTS-like symptoms. In this case, petitioner's autonomic testing was normal apart from her tilt table test, showing no evidence of small fiber neuropathy or autonomic neuropathy as seen in autoimmune autonomic ganglionopathy. Additionally, petitioner tested negative for the autoantibodies implicated by autoimmune autonomic ganglionopathy. (Tr. 459-62.) In fact, Dr. Blitshteyn acknowledges that there are no findings of any relevant

[23] Petitioner argues that Dr. Fischer "deemed a causal link between the third Gardasil vaccination on July 19, 2012, and [p]etitioner's onset of POTS to be, in effect, a diagnostic possibility." (ECF No. 118, p. 56.) Petitioner relies on Dr. Fischer's statement that "[c]oincidentally, [petitioner's] headache started a week or two after she had routine vaccines, but there was no other known trigger of illness or injury." (*Id.*; Ex. 22, p. 5.) However, Dr. Fischer did not opine that petitioner's condition was vaccine-caused; he merely noted that petitioner began experiencing headaches shortly after receiving the vaccine, and his language indicates that her onset of headaches after the vaccine was "coincidental." (*See* Ex. 22, p. 5.)

autoantibodies in this case.[24] (Ex. 44, pp. 4-5.) Although Dr. Blitshteyn indicated in her reports that she felt petitioner had small fiber neuropathy based on QSART results, Dr. Gibbons persuasively demonstrated why the QSART results did not support the presence of small fiber neuropathy. (Ex. C, p. 3; Tr. 443.) Thus, even if petitioner had successfully demonstrated at least a subset of POTS to be autoimmune in nature, these factors would still cast doubt on the idea that petitioner's own case of POTS fell within that subset.

Therefore, petitioner has failed to satisfy her burden under *Althen* prong two.

VII. Conclusion

Petitioner obviously endured a prolonged period of pain and suffering during her adolescence. For that, she has my sympathy and nothing in this decision is intended to minimize what she experienced. However, for all the reasons described above, petitioner is not entitled to compensation under the standards of this program. Therefore, this case is dismissed.[25]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[24] To be clear, testing for the adrenergic and muscarinic antibodies implicated by Dr. Blitshteyn's theory are not administered in the United States. (Ex. 44, pp. 4-5; Ex. 46, p. 5; Tr. 141-42.) As petitioner notes, this rules out any definitive statement that the presence of all possibly relevant autoantibodies have been excluded. However, it also still leaves an absence of evidence that any relevant autoantibody was actually present. In a closer case it may be appropriate to examine in greater depth why these tests are not utilized in the United States and how the fact of this unavailability of relevant testing should factor into the *Althen* prong two analysis given petitioner's burden of proof and the standard of care in this country. In this case, however, petitioner has not preponderantly established under *Althen* prong one that these antibodies are suggestive of vaccine causation or under *Althen* prong three that onset of her own condition occurred within a timeframe during which vaccine causation could be inferred based on her own theory of causation. Accordingly, even if one assumed *arguendo* that petitioner did have undetected adrenergic or muscarinic autoantibodies, that fact alone would not implicate petitioner's HPV vaccine in any logical sequence of cause and effect between the vaccination and her ultimate condition. Interestingly, the petitioner in *Balasco* did seek out this testing on her own initiative, but her own expert and treating physicians disclaimed the results because the reliability of the test was not established. *Balasco*, 2020 WL 1240917, at *28-29.

[25] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.