In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 31, 2023

GRACE DRUMMOND,	*	No. 16-702v
Petitioner,	*	Special Master Sanders
v.	*	Denial of Entitlement; Human Papillomavirus ("HPV" or "Gardasil") Vaccine; Premature Ovarian Failure/ Primary Ovarian Insufficiency ("POF/ POI"); Postural Orthostatic Tachycardia Syndrome ("POTS")
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Mark T. Sadaka, Law Offices of Sadaka Associates, LLC, Englewood, NJ, for Petitioner.
Jennifer A. Shah, United States Department of Justice, Washington, DC, for Respondent.

DECISION ON ENTITLEMENT[1]

On June 16, 2016, Grace Drummond ("Petitioner") filed a petition pursuant to the National Vaccine Injury Compensation Program ("Program" or "Vaccine Program").[2] 42 U.S.C. § 300aa-10 to 34 (2012). Pet. at 1, ECF No. 1. Petitioner alleges that she received human papillomavirus ("HPV" or "Gardasil") vaccinations on July 22, 2013, and October 23, 2013, and that these vaccines resulted in "postural orthostatic tachycardia syndrome ("POTS"),[3] and diminishing ovarian failure/insufficiency,[4] which were caused-in-fact by the above-stated vaccinations." *Id.*

[1] This Decision shall be posted 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). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to redact medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted Decision. If, upon review, I agree that the identified material fits within the requirements of that provision, such material will be withheld from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub.L. No. 99–660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Postural orthostatic tachycardia syndrome ("POTS") is "a group of symptoms (not including hypotension) that sometimes occur when a person assumes an upright position, including tachycardia, tremulousness, lightheadedness, sweating, and hyperventilation; this is seen more often in women than in men, and the etiology is uncertain." *Dorland's Illustrated Medical Dictionary* 1, 1844 (32nd ed. 2012) [hereinafter "*Dorland's*"].

[4] Premature ovarian failure, also known as primary ovarian insufficiency, is the "absence or irregularity of menses lasting at least four months, with menopausal levels of serum gonadotrophins in an adolescent girl

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On August 30, 2021, I issued a Ruling for this case and seven other petitioners who had "consolidated their claims for the purpose of determining whether they have presented a sufficient causation theory," pursuant to *Althen* prong one. *See* Findings of Fact and Conclusions of Law ("Findings of Fact") at 24, ECF No. 86; *Brayboy v. Sec'y of Health & Hum. Servs.,* No. 15-183V, 2021 WL 4453146 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). I found that the theory presented, "while not applicable to all of them, does survive *Althen* prong one, [i]n instances where a petitioner can establish by a preponderant standard that she suffers from autoimmune POI." Findings of Fact at 24. On September 21, 2022, Petitioner filed a supplemental expert report that "provided a theory of causation, based on molecular mimicry for [Petitioner's] amenorrhea, [POI,] and [POTS], related to her vaccinations of July 22, 2013, and October 23, 2013." Pet'r's Ex. 126 at 22, ECF No. 103-1. Respondent responded with three expert reports filed on November 27, 2022, and November 28, 2022. Resp't's Exs. M, N, P, ECF Nos. 107–08, 110. Petitioner's specific entitlement claim, in light of my August 30, 2021 Ruling, and the evidence submitted pursuant to *Althen* prongs two and three, is now ripe for consideration. For the reasons stated below, Petitioner's case is hereby **DISMISSED**.

I. Procedural History

Petitioner was among a group over the past several years that have filed claims alleging that they suffered POI due to HPV vaccinations. *See, e.g.*, *Culligan v. Sec'y of Health & Hum. Servs.*, No. 14-318V, 2016 WL 3101981, at *3 (Fed. Cl. Spec. Mstr. June 2, 2016) (internal citations omitted). Those cases were all contested by Respondent, who argued that many of the claims were barred from entitlement because the statute of limitations had run. *Culligan,* 2016 WL 3101981, at *3. The special master presiding over the cases at that time determined that case timeliness would depend on the onset of each petitioner's POI symptoms. *Id.*

Prior to the filing of this case, "the parties agreed that in all pending POI cases . . . an expert hearing would be held to address the question of what constitutes the first symptom or manifestation of POI onset recognized as such by the medical profession at large." *Id.* A consolidated hearing regarding the issue of onset of POI was held in June of 2015. *Id.* at *5. The lead case, *Culligan*, was dismissed as untimely, but many trailing cases were allowed to continue. *See id.*

On June 16, 2016, Petitioner filed her petition. Pet. at 1. She filed medical records on July 11, 2016. Pet'r's Exs. 1–5, ECF Nos. 7–8. On September 8, 2016, Petitioner filed a status report indicating consent "to disclosure of her case information to other POI petitioners[.]" ECF No. 13. Petitioner filed additional medical records on September 28, October 6, and November 21, 2016. Pet'r's Exs. 6–15, ECF Nos. 15–16, 19. The presiding special master held a status conference on December 1, 2016, regarding how to proceed with the remaining consolidated and newly filed POI cases. Min. Entry, docketed Dec. 1, 2016. Following the conference, in addition to agreeing that all of the POI petitioners would submit outstanding medical records, the parties agreed that they would file expert reports. Sched. Order, ECF No. 22. The parties also indicated that they would explore how to further proceed once expert reports were filed. *Id.*

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or woman under 40 years of age. It may be temporary or permanent." *Dorland's* at 945. I will refer to POF and POI interchangeably throughout this Decision.

Petitioner submitted additional medical records on December 15 and 20, 2016. Pet'r's Exs. 16–19, ECF Nos. 23–24. This case was reassigned to me on January 9, 2017. ECF No. 27. Petitioner filed medical records and a statement of completion on January 24, 2017. Pet'r's Exs. 20–21, ECF Nos. 28–29. On June 14, 2017, Petitioner filed, and I granted, a motion to substitute in a new attorney. ECF Nos. 34–35.

On August 2, 2017, Petitioner filed expert reports from Drs. Felice Gersh and Yehuda Shoenfeld. *See* Pet'r's Exs. 22–25, ECF No. 37. On September 26, 2017, and January 3, 2018, Petitioner filed supporting medical literature. Pet'r's Exs. 26–84, ECF Nos. 39–45, 47. The expert report authored by Dr. Shoenfeld was filed in support of each of the POI petitioners' cases and did not discuss case-specific information. *See* Pet'r's Ex. 25, ECF No. 37-4. Dr. Gersh's report was case-specific. *See* Pet'r's Ex. 23, ECF No. 37-2.

During a status conference I held on August 15, 2017, regarding all of the POI cases, Respondent suggested that he file an expert report addressing only the first prong of *Althen*, since all of the POI petitioners presented the same causation theory in each of the consolidated cases. Min. Entry, docketed Aug. 15, 2017; Sched. Order, ECF No. 38. I ordered Respondent to produce an expert report in accordance with his suggestion. Sched. Order at 1. Respondent filed expert reports and curricula vitae from Drs. Thomas Forsthuber, David Frankfurter, and Robert Yokel, as well as accompanying medical literature, on May 14, 2018. Resp't's Exs. A, A.1–A.31, B–F, ECF Nos. 50–55. Respondent filed additional medical literature on compact discs on June 18, 2018. Resp't's Exs. D, D Tabs 1–47, E Tabs 1–47, ECF Nos. 56–57.

On September 11, 2018, Petitioner filed responsive supplemental expert reports from Drs. Pinhas-Hamiel and Shoenfeld. Pet'r's Exs. 85–86, ECF No. 59. Petitioner filed an additional piece of medical literature on October 17, 2018. Pet'r's Ex. 87, ECF No. 60. On November 12, 2018, Petitioner filed a motion to substitute in a new attorney, which I granted on November 13, 2018. *See* ECF No. 61. Respondent filed responsive supplemental expert reports from Drs. Forsthuber, Frankfurter, and Yokel on November 19, 2018. Resp't's Exs. G–I, ECF No. 62. On December 6, 2018, Petitioner filed a motion to substitute in Petitioner's current attorney, which I granted following a status conference on December 18, 2018. *See* ECF No. 63; *see also* Min. Entry, docketed Dec. 18, 2018. Respondent filed additional medical literature on a compact disc on December 10, 2018. Resp't's Exs. D Tabs 2–3, G Tabs 1–3, H Tabs 1–23, I Tabs 1–2, ECF No. 64. On March 21, 2019, Respondent submitted an additional piece of medical literature. Resp't's Ex. J, ECF No. 69.

Petitioner filed an additional expert report from Dr. Shoenfeld on May 6, 2019, and medical literature the next day. Pet'r's Exs. 88–110, ECF Nos. 70–71. Respondent then filed medical literature on September 27, 2019. Resp't's Exs. K Tabs 1–9, ECF No. 75. The next day, Respondent filed an additional expert report from Dr. Frankfurter, along with medical literature. Resp't's Exs. L, L Tabs 1–19, ECF No. 77. Petitioner submitted additional medical literature on October 1, 2019. Pet'r's Exs. 111–112, ECF No. 78. Respondent filed a corrected version of Dr. Forsthuber's supplemental report on October 8, 2019. Resp't's Ex. K, ECF No. 81.

I held a status conference with the parties in the remaining eight consolidated POI cases on December 6, 2019. Min. Entry, docketed Dec. 6, 2019; Sched. Order at 1, ECF No. 82. Although

the facts in each case varied, the causation theory asserted was the same, and the same experts were used. Sched. Order at 1. Consequently, I proceeded to evaluate the "viability of the causation mechanism [that had been submitted in] all of these claims," pursuant to *Althen* prong one. *Id.* There was no objection from any of the parties. *Id.* The parties also agreed that the facts from one case could be used for context. *Id*. The *Brayboy* case, No. 15-183V, was ultimately selected as the lead case. *See id*. To that end, the POI petitioners again agreed to file HIPPA waivers and share medical records. *Id.* Petitioner filed her health information disclosure authorization on February 28, 2020. Pet'r's Ex. 113, ECF No. 84.

On August 30, 2021, I issued a Ruling on *Althen* prong one in all eight consolidated cases, including Petitioner's. Findings of Fact, ECF No. 86. During a status conference held on December 14, 2021, Petitioner asserted her belief that she would be able to satisfy the factors outlined in my August 30, 2021 Ruling. *See* Min. Entry, docketed Dec. 14, 2021; *see also* Sched. Order at 1, ECF No. 88. She expressed her intention to continue the prosecution of her case and file additional medical records. Sched. Order at 1. Petitioner filed an additional medical record and a status report reiterating her intention to proceed on March 15, 2022. Pet'r's Ex. 114, ECF Nos. 91–92. She submitted medical records on April 11, 2022, and August 22, 2022. Pet'r's Exs. 115–125, ECF Nos. 93, 102. Approximately one month later, Petitioner filed an expert report from Dr. David Axelrod regarding *Althen* prongs two and three and additional medical literature. Pet'r's Exs. 126–164, ECF Nos. 103–04. Respondent filed two responsive expert reports from Drs. Corrine Welt and Thomas Forsthuber, curricula vitae, and accompanying literature on November 27, 2022. Resp't's Exs. M, M Tabs 1–13, O, O Tabs 1–9, N, ECF Nos. 107–09. The following day, Respondent submitted a third report from Dr. Amy Arnold, with an accompanying curriculum vitae and literature. Resp't's Exs. P, P Tabs 1–17, Q, ECF No. 110.

II. Evidence

a. Medical History

Petitioner is a fraternal twin, born premature at 34 weeks and 3 days on September 16, 1997. *See, e.g.*, Pet'r's Ex. 23 at 1. Her relevant pre-vaccination history includes headaches, rashes, and musculoskeletal symptoms since 2009. Pet'r's Ex. 3a at 2–5, ECF No. 7-7. Her musculoskeletal symptoms included joint pain and stiffness, a left elbow injury, and multiple joint hypermobility. Pet'r's Ex. 8b at 914–15, ECF No. 19-2. A medical record dated June 24, 2010, notes an adverse skin reaction (urticaria)[5] to the varicella vaccine and an amoxicillin allergy. *Id.* at 915. Petitioner was thirteen years old at the time she began menstruating. *See, e.g.*, Resp't's Ex. M at 6, ECF No. 107-1. Petitioner was seen on February 19, 2013, for symptoms of fatigue, intermittent petechiae,[6] and elevated anti-nuclear antibodies ("ANAs").[7] Pet'r's Ex. 3a at 64. Her

[5] Urticaria is "a vascular reaction in the upper dermis, usually transient, consisting of localized edema caused by dilatation and increased capillary permeability . . . called also hives." *Dorland's* at 2011.

[6] A petechia is "a pinpoint, nonraised, perfectly round, purplish red spot caused by intradermal or submucous hemorrhage." *Dorland's* at 1422.

[7] Anti-nuclear antibodies are "antibodies directed against nuclear antigens; ones against a variety of different antigens are almost invariably found in systemic lupus erythematosus and are frequently found in rheumatoid arthritis, scleroderma (systemic sclerosis), Sjögren syndrome, and mixed connective tissue

family history is significant for adverse vaccine reactions by her twin brother. *See, e.g.*, Pet'r's Ex. 4b at 137, ECF No. 8-3. He suffered from joint swelling, syncope,[8] bradycardia,[9] and hypotension.[10] *Id*. Petitioner's mother also reported adverse reactions to vaccines and hypermobile joints. Pet'r's Ex. 11 at 3, ECF No. 19-5.

At approximately age sixteen, Petitioner received her first HPV vaccination on July 22, 2013, and her second dose on October 23, 2013, along with an influenza ("flu") vaccine. Pet'r's Ex. 3a at 1.[11]

On October 29, 2013, Petitioner was seen by her dermatologist with complaints of "scaly depigmented patches on [her] arm and face[.]" Pet'r's Ex. 2a at 5, ECF No. 7-2. The patches were first reported by Petitioner's mother via email in MyChart on October 15, 2013. *Id.* at 2.

By November 23, 2013, Petitioner was experiencing irregular menses. Pet'r's Ex. 3c at 238, ECF No. 7-9. Labs from that date showed normal follicular stimulating hormone ("FSH")[12] and luteinizing hormone ("LH")[13] levels. Pet'r's Ex. 3a at 90. Petitioner's Anti-Müllerian Hormone ("AMH")[14] was within normal range, but low, and her thyroid peroxidase and thyroglobulin antibody levels were normal. *Id.* Labs also showed normal estradiol and estrogen

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disease. Antinuclear antibodies may be detected by immunofluorescent staining. Serologic tests are also used to determine antibody titers against specific antigens." *Dorland's* at 101.

[8] Syncope is "a temporary suspension of consciousness due to generalized cerebral ischemia; called also faint[ing]." *Dorland's* at 1818.

[9] Bradycardia is "slowness of the heartbeat, as evidenced by slowing of the pulse rate to less than 60." *Dorland's* at 245.

[10] Hypotension is an "abnormally low blood pressure; seen in shock but not necessarily indicative of it." *Dorland's* at 906.

[11] Petitioner also received a flu vaccine on February 7, 2013, before her first and second doses of HPV. Pet'r's Ex. 3a at 2.

[12] The follicular stimulating hormone ("FSH") is "an anterior pituitary [] hormone that is a gonadotropic hormone[] . . . that stimulates the growth and maturation of ovarian follicles, stimulates estrogen secretion, [and] promotes the endometrial changes characteristic of the first portion (proliferative phase) of the mammalian menstrual cycle . . . ." *Dorland's* at 870. A normal FSH level for a woman still menstruating is approximately 4.7 to 21.5 IU/L, although normal value ranges may vary slightly among different laboratories. *See Follicle-stimulating hormone (FSH) blood test,* MOUNT SINAI, https://www.mountsinai.org/health-library/tests/follicle-stimulating-hormone-fsh-blood-test (last visited Mar. 7, 2023).

[13] LH levels were not measured as consistently as FSH, AMH, and estradiol ("E2"). On November 23, 2013, her levels measured within normal range at 5.9 IU/mL. Pet'r's Ex. 3c at 46. The luteinizing hormone ("LH") is an "anterior pituitary hormone that . . . acts with follicle-stimulating hormone to promote ovulation as well as secretion of androgens and progesterone. It instigates and maintains the second (secretory) portion of the mammalian estrus and menstrual cycle." *Dorland's* at 870. A normal LH level for a woman prior to menopause is 5 to 25 IU/L, although normal value ranges may vary slightly among different laboratories. *See Luteinizing hormone (LH) blood test,* MOUNT SINAI, https://www.mountsinai.org/health-library/tests/luteinizing-hormone-lh-blood-test (last visited Mar. 7, 2023).

[14] Anti-Müllerian Hormone plays a role in the development of a fetus's sex organs (primarily the uterine tubes and uterus in females and appendix testis and prostate in males) while in-utero. *Dorland's* at 870.

levels. Pet'r's Ex. 2a at 82. Petitioner's 21-hydroxylase antibodies[15] were negative/undetectable. *Id.* Her treater's impressions by December 6, 2013, included joint mobility consistent with Ehlers-Danlos type III ("EDS")[16] and post-HPV amenorrhea,[17] for which Petitioner was "undergoing further evaluation." Pet'r's Ex. 3a at 91.

Petitioner tested negative for ANAs and anti-ovarian antibodies on December 7, 2013. Pet'r's Ex. 3c at 82–83, 88. Her C3 levels[18] were low. *Id.* at 84. A pelvic ultrasound on December 11, 2013, yielded normal results. Pet'r's Ex. 3d at 74, ECF No. 8-1. On December 30, 2013, Petitioner had a follow-up regarding "coloring/duskiness" and splotches on her face. Pet'r's Ex. 2a at 9. The record from that visit also noted her brother's "recent joint swelling [and antistreptolysin O titer ("ASO")][19] of 800." *Id.* Petitioner's ASO screen and Lyme disease[20] titers were negative. *Id.* Petitioner also described stomach pains. Pet'r's Ex. 3a at 94. Petitioner's treater Dr. Joanne Taylor noted concerns that since Petitioner's first HPV vaccine, she "has had no further menses." *Id.* at 96. Dr. Taylor noted Petitioner's history of "significant reactions to vaccines in the past[,] as has her twin." *Id.* Petitioner was referred to "Dr. [Christine] Virnig for [an] immunology work[-]up secondary to concerns of [an] immune process or auto immune [sic] process being a factor in causing [Petitioner's] amenorrhea and possible ovarian failure." *Id.*

On December 24, 2013, Petitioner engaged in a phone consultation for potential patients with the Colorado Center for Reproductive Medicine. Pet'r's Ex. 16 at 27, ECF No. 23-1. She reported that "[a]fter her vaccine, she had a light period in August [of 2013], spotting in September [of 2013], with subsequently only one to two days of spotting in October and November [of 2013].

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[15] 21-hydroxylase antibodies refer to markers of autoimmune Addison's disease. *Dorland's* at 882. Addison's disease is "a chronic type of adrenocortical insufficiency, characterized by hypotension, weight loss, anorexia, weakness, and a bronzelike hyperpigmentation of the skin. It is due to tuberculosis- or autoimmune-induced destruction of the adrenal cortex, which results in deficiency of aldosterone and cortisol and is fatal in the absence of replacement therapy . . . . Called also *chronic adrenocortical insufficiency* and *primary adrenal* or *primary adrenocortical insufficiency." Id.* at 528.

[16] Ehlers-Danlos type III or Ehlers-Danlos syndrome is "a group of inherited disorders of connective tissue; formerly subdivided into ten numbered types, they have been reclassified into six descriptive types. Prominent manifestations include hyperextensible skin and joints, easy bruisability, and friability of tissues with bleeding and poor wound healing, with additional symptoms specific for individual types." *Dorland's* at 1828.

[17] Amenorrhea is the absence or abnormal stoppage of the menses. *Dorland's* at 59.

[18] C3 proteins are part of the complement system, which is part of the immune system, and protect the body from infection and illness. *Dorland's* at 393. Low levels of C3 in the blood can be signs of an autoimmune disease or a recurring bacterial infection. *See id.*; *see also C3 Complement Blood Test,* CLEVELAND CLINIC https://my.clevelandclinic.org/health/diagnostics/22138-c3-complement-blood-test (last visited Mar. 7, 2023).

[19] An antistreptolysin O titer ("ASO") is "an antibody that inhibits streptolysin." *Dorland's* at 109. Streptolysin is "an exotoxin produced by certain strains of streptococci[.]" *Id.* at 1783.

[20] Lyme disease is "a recurrent, multisystemic disorder caused by the spirochete *Borrelia burgdorferi*; vectors for human infection are the ticks *Ixodes scapularis* and *I. pacificus.* It begins in most cases with erythema chronicum migrans (at least 5 cm in diameter), often accompanied by fatigue, malaise, chills, fever, headache, and regional lymphadenopathy, followed after several weeks or months by highly variable manifestations that may include musculoskeletal pain, involvement of the heart and the nervous system, and conjunctivitis and other eye abnormalities. Persistent infection, which may last for months or years, is characterized by arthritis of large joints and, in some cases, neurologic manifestations, including chronic axonal polyneuropathy, ataxia, and spastic paraparesis." *Dorland's* at 538.

Her last full menses was in July [of 2013].” *Id.* at 28. Petitioner was concerned about premature ovarian failure and wanted to “explore future fertility preservation through oocyte vitrification.” *Id*. at 27. Petitioner was cautioned that the phone consultation “[wa]s in no way to be considered medical care or the dispersion of medical advice.” *Id.* Petitioner was assessed with POI, and a possible association with the HPV vaccines was noted. *Id.* at 28.

Petitioner was seen by Dr. Joanne Kriege on January 17, 2014, who noted that Petitioner “had post[-]HPV amenorrhea.” Pet’r’s Ex. 3a at 99. Dr. Kriege also recorded “joint hypermobility consistent with Ehlers-Danlos type III[but noted Petitioner] does not have signs on exam or on lab of a systemic autoimmune disease.” *Id.*

During a phone called placed on January 27, 2014, Petitioner’s mother reported to Dr. Taylor concerns that Petitioner “has [symptoms] related to vaccines she got in 2013[, including headache], weight loss, paresthesias, fingers turning blue, difficulty thinking[, worsening grades], fatigue and increased sleeping[,] and decreased [blood pressure].” Pet’r’s Ex. 2a at 11. Neurologist Dr. Meredith Schultz subsequently examined Petitioner on February 7, 2014, for complaints of difficulties concentrating, headaches, and tingling in her extremities. Pet’r’s Ex. 3b at 105, ECF No. 7-8. Dr. Schultz noted “several episodes of parasthesias [sic] in her feet and also a Reynaud [sic] type[21] reaction in her hands and feet,” but Dr. Schultz did not suspect “that there is any underlying neurologic damage related to vaccines.” *Id.* at 108.

A pelvic ultrasound on February 10, 2014, showed that Petitioner’s right ovary measured 2.2 cm x 1.3 cm x 1.9 cm and her left ovary measured 3.1 cm x 1.9 cm x. 2.9 cm, both within normal range. *Id.* at 144. There were multiple follicles seen within both ovaries with no suspicious growths or significant fluid accumulation. *Id.*

On February 26, 2014, Dr. Christine Seroogy from the Pediatric Immunology Clinic examined Petitioner “to see if a unifying diagnosis or insight into her medical problems can be provided from an immunologic perspective.” Pet’r’s Ex. 15 at 27, ECF No. 19-9. Dr. Seroogy noted Petitioner’s “[h]istory of reactions to vaccinations[.]” *Id.* at 29. She noted that Petitioner “has amenorrhea that temporally is correlated with receiving HPV and the influenza vaccine[; h]owever, the underlying mechanism of this remains unclear.” *Id.* Dr. Seroogy continued that Petitioner’s “estrogen levels ha[d] been normal and follicles were visualized on [her] transabdominal ultrasound.” *Id.* Additionally, Petitioner “has no clinical or laboratory evidence of autoimmune-mediated ovarian failure or other autoimmune endocrine problems.” *Id.* at 30. Dr. Seroogy referenced Petitioner’s negative testing for anti-21 hydroxylase antibodies, thyroid antigen autoantibodies, and normal LH, FSH, and estradiol levels. *Id.* at 28. She opined that “[t]here is no medical evidence to support a causal relationship between vaccinations and POI,” and she found none in Petitioner’s case. *Id.* at 29.

Petitioner was seen by Dr. Gisela Chelimsky at the Children’s Hospital of Wisconsin Autonomic Reflex Laboratory on May 12, 2014. Pet’r’s Ex. 4a at 26, ECF No. 8-2. The listed history recorded “Ehlers-[D]anlos with recent development of multiple medical issues/sympttoms [sic].” *Id.* Dr. G. Chelimsky noted that Petitioner’s mother believed Petitioner’s amenorrhea stemmed from the HPV vaccine. *Id.* Dr. G. Chelimsky documented symptoms of dysautonomia in Petitioner’s record from this visit, including instances “where her heart rate will drop very low for

[21] Raynaud’s phenomenon is “intermittent bilateral ischemia of the fingers, toes, and sometimes ears and nose, with severe pallor and often paresthesias and pain[.]” *Dorland’s* at 1430.

several hours[,]" randomly dilated pupils, and brain fog. *Id.* Petitioner underwent a tilt test,[22] which was mildly abnormal. *Id.* at 28–31. Dr. G. Chelimsky recorded, "1) a pre-syncopal episode; 2) no evidence of postural tachycardia syndrome; 3) normal cardiac sympathetic and parasympathetic function; [and] 4) no evidence of an autonomic neuropathy." *Id.* at 31.

Dr. Thomas Chelimsky, also with Children's Hospital of Wisconsin's Autonomic Reflex Laboratory, saw Petitioner on August 5, 2014. *Id.* at 83. Dr. T. Chelimsky noted Petitioner's past diagnoses including hypermobility syndrome, dizziness, elbow dysplasia, and chronic constipation. *Id.* at 85. He wrote that Petitioner presented with "post HPV vaccine near syncope and migraine with POTS by [autonomic nervous system ("ANS")] testing." *Id.* at 86. Dr. T. Chelimsky found that "[t]he salient feature of her presentation appears to be excessive lability of many vegetative processes, including heart rate, estrogen levels (by history)[,] and weight." *Id.* He noted his impression that this was "some type of central autonomic instability[, but he was n]ot sure if this [wa]s lesion[-]based or perhaps an auto-immune [sic] process?" *Id.* Petitioner was diagnosed with POTS, syncope, and variant migraines. *Id.*

A note from a telephone encounter between Petitioner's mother and both Drs. G. and T. Chelimsky from August 11, 2014, showed Petitioner "had several unusual symptoms this past week, including [approximately] 48 [hours] of twitching of her right arm, left eyelid[,] and lower lip," as well as a "severe restless legs" feeling in her entire body, which "kept her awake for most of the night." Pet'r's Ex. 4b at 137. Petitioner's mother continued that "[t]wo days later[,]" she had "a more pronounced episode of pallor, duskiness of [her] face, lips, and hands, [and] dizziness," followed by feeling "out of it[,]" cold in 70–80 degree Fahrenheit weather, sensitivity to sound and light, brain fog, fatigue, and increased irritability. *Id.*

Dr. Paul Reber performed an endocrinology evaluation on August 26, 2014, due to Petitioner's reduction in menses, orthostasis,[23] and 17-pound weight loss from May to December of 2013. Pet'r's Ex. 3b at 142. An anti-ovarian antibody test was negative. *Id.* at 143. Petitioner reported suffering from headaches, lightheadedness, and nausea. *Id.* at 142. An assessment included "reduced menses, orthostatic hypotension, and unintentional weight loss [in a 16-year-old] with a history of joint hypermobility/possible Ehlers[-]Danlos type III." *Id.* at 145. Dr. Reber noted "that [Petitioner] ha[d] regained her weight," but indicated a "till [sic] table test [was] consistent with autonomic dysfunction/POTS." *Id.* at 144–45. Petitioner continued to complain of dysautonomia symptoms through 2014 and 2015, including an irregular heartrate, Pet'r's Ex. 2b at 2, ECF No. 7-3; bradycardia with a drop in blood pressure, Pet'r's Ex. 4b at 192; and "dizziness, pallor/duskiness, [and] simultaneous low pulse and [blood pressure]." Pet'r's Ex. 2c at 194, ECF No. 7-4.

On May 29, 2015, Petitioner returned to Dr. Kriege for a follow-up. Pet'r's Ex. 3b at 168. She noted Petitioner had "post-HPV amenorrhea – now improved." *Id.* Dr. Kriege indicated that

[22] A tilt test is the "measurement of various bodily responses while the patient is tilted to different angles on a tilt table, usually head up, such as monitoring of circulatory, cardiac, and neurologic responses." *Dorland's* at 1901.

[23] Orthostasis or orthostatic hypotension refers to "a fall in blood pressure associated with dizziness, blurred vision, and sometimes syncope, occurring upon standing or when standing motionless in a fixed position; it can be acquired or idiopathic, transient or chronic, and may occur alone or secondary to a disorder of the central nervous system." *Dorland's* at 906.

Petitioner was experiencing regular menses with low AMH levels, subject to monitoring. *Id.* at 169. Dr. Kriege did not see "signs on exam or lab of a systemic autoimmune disease." *Id.*

Petitioner's labs from June 1, 2015, showed that "all antibody labs ha[d] returned negative (including anti-ovarian), which [sic] exception of mildly elevated ANA (very nonspecific)." Pet'r's Ex. 2d at 36, ECF No. 7-5. Her growth hormone and thyroid labs were normal. *Id.* Petitioner's AMH was normal at 1.4, along with her T4 Free, thyroid stimulating hormone, and complete blood count levels. Pet'r's Ex. 3d at 48–51. Her 21-hydroxylase, thyroid peroxidase, and thyroglobulin antibodies were also negative. *Id.* at 58, 63–64. A pelvic ultrasound performed the same day showed Petitioner's right ovary measured 2.1 x 1.5 x 1.8 cm and her left ovary measured 2.0 x 1.8 x 1.6 cm. Pet'r's Ex. 3b at 73. A June 3, 2015 note from Petitioner's mother to Dr. Reber reports that Petitioner had a "weakly positive [ANA] (1.5), which we know is nonspecific." Pet'r's Ex. 2c at 58, 61; Pet'r's Ex. 3d at 54.

Reproductive specialist Dr. David Olive wrote a letter, dated June 19, 2015, expressing "considerable concern that [Petitioner's decreased ovarian reserve] may progress to primary ovarian insufficiency." Pet'r's Ex. 7 at 1, ECF No. 16-1. Petitioner had sought out Dr. Olive for information regarding egg retrieval. *Id.* A July 14, 2015 medical record, signed by Dr. Minjarez from the Colorado Center for Reproductive Medicine, stated that Petitioner had progressed to POI. Pet'r's Ex. 16 at 20. The record also noted, however, that Petitioner's 2013 AMH levels had improved over the last two years, and as of June 11, 2015, Petitioner's "cycles ha[d] returned regularly, every 26–27 days." *Id.* at 21, 25. The record continued that Petitioner "ha[d] been evaluated by neurology, rheumatology, and hematology with no definitive diagnosis." *Id.* at 25. Petitioner continued regular testing for evidence of autoimmune disease throughout 2015 and 2016. Testing for anti-adrenal antibodies was negative on January 4, 2016. Pet'r's Ex. 6 at 1, ECF No. 15-1.

On July 18, 2016, Petitioner was seen by Dr. Don Bukstein for her "extraordinarily complex history revolving around reactions to multiple vaccines," and "immediate concerns [of] symptoms and objective testing suggesting ovarian failure following an HPV vaccine." Pet'r's Ex. 19 at 1, ECF No. 24-2. Dr. Bukstein stated his belief that Petitioner's easy bruising and petechia is a "blood vessel problem[,] secondary to a type of metabolic connective tissue disease, possible Ehlers-Danlos syndrome, type 3, rather than immunologically mediated." *Id.* He did not rule out an autoimmune etiology for her ovarian problem and noted an ongoing investigation into "the possibility of ovarian antibodies or other antibodies in signaling or even causing this disorder." *Id.* Dr. Bukstein advised that, "for the near future[,]" Petitioner "should NOT receive any vaccines of any sort." *Id.* (emphasis in original).

Approximately two years later, on June 18, 2018, Petitioner presented to St. Mary's Hospital with complaints of vertigo[24] with ataxia.[25] Pet'r's Ex. 121 at 294, ECF No. 102-6. An MRI "revealed a left cerebellar peduncle lesion (small)[,] which generated concern for [a] possible demyelinating process [versus] a small ischemic[26] workup." *Id.* at 296. Anticardiolipin, lupus

[24] Vertigo is "an illusory sense that either the environment or one's own body is revolving; it may result from diseases of the internal ear or may be due to disturbances of the vestibular centers or pathways in the central nervous system." *Dorland's* at 2051.

[25] Ataxia is "failure of muscular coordination; irregularity of muscular action." *Dorland's* at 170.

[26] Ischemia generally refers to the "deficiency of blood in a part, usually due to functional constriction or actual obstruction of a blood vessel." *Dorland's* at 961.

anticoagulant, and beta-2 glycoprotein testing yielded negative results; and her ANA, ANCA, and complement levels were normal. *Id.* Neuroimmunologist Dr. Paul Robelia recommended against inpatient admission because "she did not meet criteria," based on her improving symptoms, but he referred Petitioner to an outpatient neuroimmunology clinic for follow up. *Id.* Laboratory testing done on June 29, 2018, revealed anti-α-1-adrenergic and anti-muscarinic cholinergic receptor 3 antibodies. Pet'r's Ex. 114 at 1–2, ECF No. 91-1.

On June 20, 2019, Petitioner was seen for a follow-up by Dr. Matthew Raday. Pet'r's Ex. 121 at 508. He reviewed Petitioner's MRI images and found them to be "most consistent with an acute ischemic stroke."[27] *Id.* On August 28, 2019, Dr. Mary Hintermeyer at Children's Hospital of Wisconsin evaluated Petitioner for recurrent infections. Pet'r's Ex. 119 at 1, ECF No. 102-4. She did "not feel that [Petitioner] has an underlying immune deficiency disorder." *Id.* at 10. Dr. Hintermeyer assessed Petitioner with POTS, prior Epstein-Barr virus infection,[28] rhinitis,[29] GERD,[30] and constipation. *Id.*

Petitioner underwent extensive lab testing on March 14, 2022, that showed she was "at risk" for anti-AT1R antibodies and anti-ETAR antibodies. Pet'r's Ex. 115 at 1, ECF No. 93-1. Petitioner was also positive for anti-α-1-adrenergic antibodies, anti-ß-1 and anti-ß-2-adrenergic antibodies, anti-muscarinic cholinergic receptor-3 and 4 antibodies, anti-TSHDS-IgM-antibodies, anti-ACE-2-antibodies, and anti-MAS1-antibodies. *See id.* An ovarian assessment report dated August 2, 2022, revealed normal AMH, FSH, LH, and estradiol levels, and a "good" egg retrieval score. Pet'r's Ex. 125 at 1, ECF No. 102-10. Petitioner has not filed additional medical records.

b. Petitioner's Hormone Tests Results[31]

DATE	**FSH**	**AMH**	**Estradiol**
(reference range)[32]	*3.0-14.4 IU/L*	*.7-3.5 ng/mL*	*<84 pg/mL*
11.23.2013	4.9 IU/L	1.5 ng/mL	97 pg/mL
12.07.2013		1.43 ng/mL	
12.27.2013			246 pg/mL
01.01.2014		1.42 ng/mL	
01.13.2014	10 IU/L		82 pg/mL
02.01.2014	4.2 IU/L	1.72 ng/mL	62 pg/mL

[27] An ischemic stroke is stroke syndrome caused by ischemia of an area of the brain. *Dorland's* at 1786. Stroke syndrome is "a condition with sudden onset caused by acute vascular lesions of the brain, such as infarction from hemorrhage, embolism, or thrombosis, or rupturing aneurysm. It may be marked by any of a variety of symptoms reflecting the focus of infarction or hemorrhage, including hemiparesis, vertigo, numbness, aphasia, and dysarthria; it is often followed by permanent neurologic damage." *Id.* at 1849.

[28] Epstein-Barr is "a virus of the genus *Lymphocryptovirus* that causes infectious mononucleosis[.]" *Dorland's* at 2061.

[29] Rhinitis is "inflammation of the mucous membrane of the nose." *Dorland's* at 1639.

[30] GERD (gastroesophageal reflux disease) is "any condition noted clinically or histopathologically that results from gastroesophageal reflux, ranging in seriousness from mild to life-threatening; principal characteristics are heartburn and regurgitation." *Dorland's* at 533.

[31] These labs were all drawn after Petitioner's second HPV vaccine and flu vaccine administered on October 23, 2013.

[32] *See* Pet'r's Ex. 7 at 6.

02.21.2014	4.7 IU/L	1.8 ng/mL	109 pg/mL
05.16.2014		2.6 ng/mL	
11.26.2014		2.8 ng/mL	
05.23.2014		1.0 ng/mL	
06.01.2015	4.5 IU/L	1.4 ng/mL	31 pg/mL
06.29.2015	4.75 IU/L	1.1 ng/mL	53 pg/mL
07.14.2015		1.9 ng/mL	
08.02.2022	8.49 IU/L	1.58 ng/mL	45.8 pg/mL

c. Petitioner's Status Reports

On March 15, 2022, Petitioner filed a status report that indicated her intention to rely on her clinical presentation along with positive antibody testing to establish an autoimmune etiology for her POI. ECF No. 92. A June 15, 2022 status report specified that on June 29, 2018, Petitioner tested positive for anti-α-1-adrenergic and anti-muscarinic cholinergic receptor 3 antibodies. ECF No. 97 (citing Pet'r's Ex. 114). It further specified that on March 14, 2022, Petitioner underwent additional testing, which showed positive results for eight different types of autoantibodies. *Id.* (citing Pet'r's Ex. 115).

III. Expert Review[33]

A. Petitioner's Expert, Felice Gersh, M.D.

Dr. Gersh received her medical degree from the University of Southern California School of Medicine in 1977. Pet'r's Ex. 22 at 1, ECF No. 37-1. She completed her internship and residency in obstetrics and gynecology at Kaiser Hospital in Hollywood, California in 1981. *Id.* Dr. Gersh then completed a fellowship in integrative medicine at the University of Arizona in 2012. *Id.* She has worked in private practice and as the medical director for the Integrative Medical Group of Irvine since 1981. *Id.* at 2. Her prior experience also includes serving as an assistant clinical professor at the University of Southern California. *Id.* at 3. Dr. Gersh is board certified in obstetrics and gynecology. *Id.* at 1. Her areas of expertise include polycystic ovary syndrome, endometriosis, uterine fibroids, menstrual irregularity, and the effects of environmental toxins on female reproductive and gynecological health. *Id.*

B. Petitioner's Expert, David Axelrod, M.D.

Dr. Axelrod received his medical degree from the University of Michigan Medical School in 1974. Pet'r's Ex. 126 at 1, ECF No. 103-1. Dr. Axelrod is a "[c]linical [i]mmunologist, trained at McGill University . . . and at the National Institutes of Health[.]" *Id.* The focus of his training at these institutions was in allergy and rheumatology. *Id.* He has held several academic appointments, including serving as the academic chief in the division of allergy, and later the head of clinical research, at the Mount Carmel Mercy Hospital in Detroit, Michigan from 1984 to 1989, and then

[33] This Decision is limited to a discussion of *Althen* prongs two and three, and the expert reports authored in support thereof. I therefore do not find it necessary to re-address the reports authored in support of *Althen* prong one, or the qualifications of the experts that opined on that factor only, unless the expert also authored reports on prongs two and three. *See generally* Findings of Fact, ECF No. 86.

as an associate professor of adult rheumatology at the Medical College of Ohio until 1991. *Id.* at 2. He joined the faculty at New Jersey Medical School as an associate professor in the division of allergy, immunology, and rheumatology in 2007, and served as the interim director of the same division from 2009 until 2010. *Id.* During his clinical practice from 1991 until his retirement in 2018, he "was involved with the diagnosis and treatment of individuals with drug reactions (including to vaccines)." *Id.* He holds memberships in numerous medical societies related to allergy, immunology, and rheumatology. Pet'r's Ex. 127 at 2, ECF No. 103-2. His curriculum vitae contains approximately twenty-seven publications and abstracts of which he is a listed author. *See id.* at 3–4.

C. Respondent's Expert, Thomas Forsthuber, M.D.

Dr. Forsthuber received medical and doctoral degrees from the University of Tübingen in Germany between 1987 and 1989. Resp't's Ex. B at 1, ECF No. 53-3. He completed post-doctoral programs at the University of Mainz in Germany, the University of California at Los Angeles's department of microbiology and molecular genetics, and Case Western Reserve University. *Id.* at 3. Dr. Forsthuber has been a professor of immunology in the University of Texas ("UT") at San Antonio's department of biology since 2005. *Id.* He is also an adjunct professor of pathology and of microbiology and immunology at the UT Health Sciences Center. *Id.* He currently serves in editorial positions on multiple journals, including, for example, *Clinical Immunology* as well as *Autoimmunity*. *Id.* at 10. He is a listed author on approximately eighty-five articles and four book chapters as well as numerous abstracts. *Id.* at 19–27, 32–41. Much of Dr. Forsthuber's research is focused on autoimmunity and related topics. *See id.*

D. Respondent's Expert, Corinne Welt, M.D.

Dr. Welt received her medical degree from Cornell University Medical College in 1991. Resp't's Ex. M at 1. She completed post-doctoral training at the Brigham and Women's Hospital in internal medicine from 1991 to 1994. *Id.* Dr. Welt then completed fellowships in endocrinology and reproductive endocrinology at Massachusetts General Hospital and Harvard Medical School until 1997. *Id.* From there, she served on the faculty at Massachusetts General Hospital in the reproductive endocrine unit. *Id.* Dr. Welt has been a professor of internal medicine (endocrinology and metabolism) at the University of Utah since 2014. *Id.* She has served as the chief of the endocrinology, metabolism, and diabetes division at the same institution since 2019. Resp't's Ex. N at 1, ECF No. 109-1. Dr. Welt has held several editorial and reviewer positions on journals regarding reproduction, endocrinology, and metabolism. *Id.* at 2. She is also a member of numerous professional organizations and scientific activities related to endocrinology, POF, and infertility. *Id.* at 4–6. Dr. Welt's curriculum vitae lists over 135 articles, books, book chapters, and abstracts, of which she is a listed author. *Id.* at 9–30.

Dr. Welt's medical focus involves ovulatory disorders in women, including POI. Resp't's Ex. M at 1. She is currently a "key investigator [of POI,] coining the name change [from POF] . . . and leading [] research examining the etiology of POI and reviewing POI diagnostic criteria and treatment." *Id.* She actively serves as a treating physician in the field of reproductive endocrinology in Salt Lake City, UT. Resp't's Ex. N at 1. She has seen "over 100 women with POI" and has "identified the cause of POI in multiple women[.]" Resp't's Ex. M at 1.

E. Respondent's Expert, Amy Arnold, Ph.D.

Dr. Arnold received her doctorate degree in physiology and pharmacology from Wake Forest University in 2009. Resp't's Ex. Q at 1, ECF No. 110-19. She later received a master of science degree in clinical investigation from Vanderbilt University in 2014. *Id.* Dr. Arnold completed a fellowship at the Vanderbilt Autonomic Dysfunction Center. Resp't's Ex. P at 1, ECF No. 110-1. She currently serves as an associate professor in the department of neural and behavioral sciences at the Pennsylvania State University College of Medicine. *Id.* Dr. Arnold has published seventy-four peer-reviewed manuscripts, of which, over thirty are related to the diagnosis, pathophysiology, and treatment of cardiovascular autonomic disorders, including POTS, orthostatic hypotension, and primary autonomic failure. *Id.* She is on the editorial boards for *Clinical Autonomic Research, Hypertension,* and *Autonomic Neuroscience: Basic and Clinical. Id.* at 2. She has also participated in a national working group that created the 2020 Report to the National Institute of Health entitled: "Postural Orthostatic Tachycardia Syndrome: State of the Science, Clinical Care, and Research." *Id.* at 1. Dr. Arnold has also received research grants to understand the prevalence of hypermobile EDS in POTS. *Id.*

IV. Petitioner's Expert Reports[34]

A. Dr. Felice Gersh

Dr. Gersh provided a very brief summary of Petitioner's medical history, which she described as "quite complicated." Pet'r's Ex. 23 at 1. She noted Petitioner's EDS diagnosis, "numerous issue [sic] with her joints," skin conditions, and numerous infections. *See id.* Dr. Gersh also referenced Petitioner's family history of adverse vaccine reactions, as well as her mother's fertility difficulties and menstrual dysfunction. *Id.* Despite this family history, Dr. Gersh opined that Petitioner's ovarian dysfunction is tied to her HPV vaccination. *See id.* at 1–2. Post vaccination, Petitioner's estrogen levels were measured regularly, but "varied from a high to a relatively low level." *Id.* at 1. Dr. Gersh asserted that Petitioner's AMH level was borderline low initially, [and] ultimately [became] significantly low," as well as her antral follicle count, "indicat[ing] the development of [POI]." *Id.* Dr. Gersh explained that because Petitioner was born premature, she was "prone to developing abnormal microbiomes of [her] intestinal tract, which predispose[d her] to a myriad of risks involving [her] developing immune system[]." *Id.* at 2. Dr. Gersh concluded it is "very medically probable that the development of the ovarian insufficiency was strongly connected to the poorly developed intestinal microbiome placing her at an increased risk, with the HPV vaccine functioning as the final link in altering the immune system . . . resulting in [POI]." *Id.*

B. Dr. David Axelrod

[34] Petitioner filed expert reports authored by Drs. Yehuda Shoenfeld and Orit Pinhas-Hamiel, outlining her proposed general causation theory. Pet'r's Exs. 23, 25. These reports were filed in eight cases consolidated for the purpose of determining whether the POI petitioners presented a sufficient causation theory pursuant to *Althen* prong one. My determination, contained in a Ruling issued on August 30, 2021, discussed these reports in detail. I will not re-litigate those resolved issues here, although the reports may be referenced as necessary. This Decision is specific to this Petitioner's case and applies my findings from the general causation Ruling to the evidence presented herein on *Althen* prongs two and three.

Dr. Axelrod began his report with a list of relevant notations in Petitioner's medical history. Pet'r's Ex. 126 at 1–2. He noted that pre vaccination, on January 11, 2013, Petitioner "had a weakly positive [ANA]" test result. *Id.* at 2. He noted that on November 8, 2013 (approximately two weeks after Petitioner's second HPV vaccine), Petitioner's mother reported that her daughter's menstrual cycles had become irregular in August of 2013 (the month after Petitioner's first HPV vaccination). *Id.* at 3. She further reported that Petitioner's cycles had stopped completely in October, immediately following the second HPV vaccination. *Id.* Dr. Axelrod acknowledged that Petitioner's cycles began again in 2014; however, he noted her mother's report that "they were now anovulatory." *Id.* at 4 (citing Pet'r's Ex. 3b at 105–08). He also referenced Dr. Schultz's neurology report that indicated Petitioner's treaters were concerned that Petitioner had EDS. *Id.* at 1–2.

Dr. Axelrod expanded on Petitioner's causation theory for POI. *See id.* at 13–16. He provided a general explanation of molecular mimicry supported by filed literature.[35] *Id.* at 13 (citing Pet'r's Exs. 128, 140–41, ECF Nos. 104-1, 104-13–104-14).[36] He wrote that he "support[s] the molecular mimicry theory outlined therein by Dr. Shoenfeld that was shown to be sound and reliable by the Court. However, in this case, [Petitioner] has multiple positive autoantibodies and a condition, [EDS,] that deserve further comment and analysis." *Id.*

Dr. Axelrod acknowledged that "the optimal length for peptides to [cross-react during a molecular mimicry process] may be 8–12 amino acids," but he argued that "Hemmer et al.[37] showed that even small peptides (3–5 amino acids in length) could result in [autoimmune] responses." *Id.* at 14 (citing Pet'r's Ex. 145 at 1, ECF No. 104-18). The Hemmer et al. article aimed to examine and challenge minimal peptide length requirements "for activation of CD4+ HLA class II restricted T cells." Pet'r's Ex. 145 at 1. The study revealed that "shorter peptides may be sufficient in certain instances, although at much higher concentrations." *Id.* at 2. The authors suggested that the study may have implications for our understanding of "the potential for cross-reactivity in the immune system." *Id.* at 1.

The Frankild et al.[38] article was also referenced by Dr. Axelrod to argue that "amino acid similarity, not identity, is a predictive measure of cross-reactivity." Pet'r's Ex. 126 at 14 (citing Pet'r's Ex. 146, ECF No. 104-19). This article is a study of cytotoxic T cell cross-reactivity, and the authors found that "seemingly distinct T cell epitopes, i.e., ones with low sequence identity,

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[35] A detailed review of the general mechanics of molecular mimicry will not be included in this Decision. The parties have already presented detailed arguments on the merits of molecular mimicry generally, and in these cases alleging HPV vaccine-caused POI. As I have repeatedly admonished, I will not continue to relitigate the merits of my findings on *Althen* prong one. I have included an abbreviated recitation of any additional arguments that the parties have presented and my consideration and analysis of said arguments where appropriate herein.

[36] *See, e.g.*, ABUL K. ABBAS et al., CELLULAR & MOLECULAR IMMUNOLOGY 1–11 (Elsevier eds., 9th ed. 2018); D. Kanduc et al., *Massive peptide sharing between viral and human proteomes,* 29 PEPTIDES 1755–66 (2008); B. Trost et al., *Bacterial peptides are intensively present throughout the human proteome,* 1:1 SELF/NONSELF 71–74 (2010).

[37] B. Hemmer et al., *Minimal peptide length requirements for CD4+ T cell clones – implications for molecular mimicry and T cell survival,* 12(3) INT. IMMUNOL. 375–83 (2000).

[38] S. Frankild et al., *Amino Acid Similarity Accounts for T Cell Cross-Reactivity and for "Holes" in the T Cell Repertoire,* 3(3) PLOS ONE 1831–39 (2008).

are in fact more biochemically similar than expected." Pet'r's Ex. 146 at 1. Furthermore, the authors noted that cytotoxic T cells "have the tendency to respond mostly to peptides that do not resemble self-antigens." *Id.*

Dr. Axelrod opined that Petitioner "developed a protective immune reaction to her Gardasil [and flu] injections." Pet'r's Ex. 126 at 15. She "developed an inflammatory response consistent with both a primary adaptive immune response and a secondary adaptive immune response . . . with a clinical picture of irregular periods," followed by amenorrhea after the second Gardasil injection. *Id.* This immune response was the catalyst for a molecular mimicry process that caused her to develop "blocking antibodies to her [AMH] to account for her clinical picture." *Id.* at 15–16.

Dr. Axelrod focused on Petitioner's AMH levels because AMH "regulates the number of growing follicles and their selection for ovulation." *Id.* at 8. He asserted that "[AMH] levels are considered a predictor of [POI]," and "[l]ow [AMH] levels [in] women result[] in a lower number of retrievable oocytes, irrespective of [] FSH levels." *Id.* In support, he filed several articles that discuss AMH in reproductive health. *See id.* (citing Pet'r's Exs. 130–31, ECF Nos. 104-3–104-4).[39] The Bedenk et al.[40] article, for example, is a review of the value of AMH as a predictor "in assessing the ovarian reserve, which can lead to a better efficiency of in vitro fertilization ["IVF")] procedures." Pet'r's Ex. 129 at 1, ECF No. 104-2. The Xu et al.[41] study focused on the "role of AMH during follicular development in vivo in nonhuman primates." Pet'r's Ex. 132 at 8, ECF No. 104-5. Researchers concluded that "follicle growth patterns and corresponding steroid hormone production were altered by AMH protein supplementation or [by] blocking endogenous AMH action." *Id.*

Dr. Axelrod identified a series of amino acid sequences in the Gardasil and influenza vaccines that contain one or more peptides found in AMH strain, P03971. Pet'r's Ex. 126 at 14. He noted that the Tuohy and Altuntas[42] article "suggest[s] that MATER [protein] and [alpha]-enolase [enzyme] are target antigens for autoimmune [POI]." *Id.* (citing Resp't's Ex. K, Tab 9 at 1, ECF No. 75-9). Dr. Axelrod also identified similarities in amino acid sequences of 3–7 conserved amino acids between these two antigens and components of Gardasil. *Id.* at 16. He argued that this homology is sufficient to incite a molecular mimicry cross-reaction capable of causing the development of POI. *Id.* at 16–17.

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[39] *See, e.g.*, L. Moolhuijsen et al., *Anti-Müllerian Hormone and Ovarian Reserve: Update on Assessing Ovarian Function,* 105:11 J. CLIN. ENDOCRIN. & METABOL. 3361–73 (2020); A. La Marca et al., *Anti-Müllerian hormone (AMH) in female reproduction: is measurement of circulating AMH a useful tool?,* 64 CLIN. ENDOCRIN. 603–10 (2006).

[40] J. Bedenk et al., *The role of anti-Müllerian hormone (AMH) in ovarian disease and infertility,* 37 J. ASSISTED REPRODUCT. & GEN. 89–100 (2020).

[41] F. Xu et al., *Stage-dependent actions of antimüllerian hormone in regulating granulosa cell proliferation and follicular function in the primate ovary,* 1(2) F. S. SCI. 161–71 (2021).

[42] V. Tuohy & C. Altuntas, *Autoimmune and premature ovarian failure,* 19 CURR. OPIN. OBSTET. GYNECOL. 366–69 (2007).

Petitioner eventually "developed a number of antibodies with reactivity to auto-antigens," including fibroblast growth factor,[43] which Dr. Axelrod asserted is associated with POTS. *Id.* at 12. He asserted that there is similar amino acid sequencing between fibroblast growth factor receptor 3 peptides and the L1 protein from HPV strain 6 within the Gardasil vaccine. *Id.* This homology is also sufficient, according to Dr. Axelrod, for a cross-reaction leading to the development of POTS. *Id.* at 17.

After identifying homology within the peptide sequences, Dr. Axelrod applied his theory of molecular mimicry to Petitioner's case. He argued that Petitioner "had within her immune system lymphocytes capable of reacting to her [AMH]." *Id.* at 16–17. He continued that Petitioner "eventually developed antibodies to autoantigens related to autoimmune [POI] and [POTS], indicating that her immune system lymphocytes are capable of reacting to her ovaries and autonomic myelinated and unmyelinated neurons." *Id.* at 17. This production of antibodies "prevent[ed] her [AMH] from its physiologic function of providing ovarian follicular reserve." *Id.*

Citing the Kirshenbaum et al.[44] article, Dr. Axelrod discussed the clinical presentation of POI and noted that "while follicular depletion might be the consequence of non-autoimmune causes, it may also be the final stage of an autoimmune disease." *Id.* at 10 (citing Pet'r's Ex. 136, ECF No. 104-9). Kirshenbaum et al. stated "that autoimmune causes of [POI] should be suspected in the presence of anti-ovarian antibodies, lymphocytic oophoritis or any associated autoimmune disorder." Pet'r's Ex. 136 at 2. Dr. Axelrod also cited the Komorowska[45] article that cautioned, "[b]y the time a woman is diagnosed [with POI], she has [often] exhausted her follicular supply and, presumably, also the target antigen for the autoimmune attack on her ovary." Pet'r's Ex. 137 at 2, ECF No. 104-10. Komorowska concluded, "[t]hus, the autoimmunity causal of POI can be difficult to detect retrospectively." *Id.* Dr. Axelrod argued that in these POI cases, "anti-ovarian antibodies cannot be found," despite an autoimmune etiology. Pet'r's Ex. 126 at 10.

The Jankowska[46] article relied upon by Dr. Axelrod identifies vaccination as a potential cause of POI and noted that these patients "showed low levels of [estradiol] and increased FSH and LH and specific auto-antibodies (antiovarian and antithyroid), suggesting that the HPV vaccine triggered an autoimmune response." Pet'r's Ex. 135 at 3, ECF No. 104-8. Dr. Axelrod referenced Petitioner's March 17, 2022 positive antibody results, but noted that "she did not have evidence of any of the diseases associated with these autoantibodies." Pet'r's Ex. 126 at 10–11. He noted her consistently normal FSH, LH, and estradiol levels. *Id.* at 11. He also noted her progesterone levels and normal inhibin B levels. *Id.* He stated that "she did not suffer from hot flashes, night sweats, excessive sweating or hair loss." *Id.* Dr. Axelrod opined that "it is not clear that [Petitioner] suffered from [POI]." *Id.* He continued, "[h]owever, given the transient loss of her menstrual periods following her first Gardasil injection, [and a sustained] loss of her menstrual

[43] Fibroblast growth factor is "a family of structurally related polypeptides that act as signaling molecules [that] are involved in a wide range of biological functions, regulating cellular proliferation, survival, migration, and differentiation. Usually mitogens, they also have regulatory, morphologic, and endocrine effects." *Dorland's* at 870.

[44] M. Kirshenbaum & R. Orvieto, *Premature ovarian insufficiency (POI) and autoimmunity – an update appraisal,* 36 J. ASSISTED REPRODUCT. & GEN. 2207–15 (2019).

[45] B. Komorowska, *Autoimmune premature ovarian failure,* 15(4) MENOPAUSE REV. 210–14 (2016).

[46] K. Jankowska, *Premature Ovarian Failure,* 16(2) MENOPAUSE REV. 51–56 (2017).

periods following her second Gardasil injection, as well as the low complement C3 level, in the face of a normal complement C4 level,"[47] he argued this "suggests an immune cause to her [amenorrhea]." *Id.*

Ultimately, Dr. Axelrod reasoned that the HPV vaccines "activated [Petitioner's] lymphocytes, specific for her [AMH], with the production of antibodies to her [AMH], which resulted in the loss of early growing follicles and the loss of her ability to ovulate and have normal menses." *Id.* at 9. He further opined that the antibodies, "blocked the interaction of [AMH] with its receptor [Anti-Müllerian Hormone receptor type 2 ("AMHRII")] and interfered with its detection in the blood." *Id.* However, the blocking antibodies "did not fix[,] complement or direct cytotoxic cells . . . to cause inflammatory damage to [Petitioner's] ovaries." *Id.*

The 2018 and 2022 autoantibody results indicate to Dr. Axelrod that Petitioner "has lymphocytes with receptors to these proteins that have escaped central thymic [and potentially] peripheral selection (regulation), perhaps through exposure to peptides with similar conserved amino acids, such as the Gardasil and [i]nfluenza vaccines." *Id.* at 12. Despite his initial equivocation, Dr. Axelrod ultimately found support for an autoimmune POI diagnosis in Petitioner. *Id.* He noted the proximity of Petitioner's ovarian problems to, what he considered, "both a challenge and rechallenge to the Gardasil vaccinations, and given that she received an influenza vaccination ([with a likely history of exposure to influenza]), with evidence of complement activation." *Id.*

In Dr. Axelrod's opinion, Petitioner's EDS made it more likely that she suffered from POTS. *Id.* Dr. Axelrod noted Petitioner's autonomic symptoms began after her first HPV vaccine. *Id.* He then cited the Brooks et al.[48] study's finding that not only were EDS subjects more likely than controls to suffer from autonomic dysfunction, "they were more likely to suffer from [POTS] than their controls." *Id.* (citing Pet'r's Ex. 139, ECF No. 104-12). Dr. Axelrod acknowledged that this correlation "does not prove that either [EDS] or [POTS] are autoimmune." *Id.*

The appropriate timeframes, identified by Dr. Axelrod, for the primary adaptive immune response and secondary adaptive response that evolves into molecular mimicry is 2–3 days and 14 days, respectively. *Id.* at 18 (citing Pet'r's Ex. 128, ECF No. 104-1).[49] Dr. Axelrod cited to Lawley et al.'s[50] study of serum sickness, which noted that "serum sickness has long been presumed to be mediated by the formation of circulating immune complexes composed of host antibody and foreign antigenic proteins." Pet'r's Ex. 147 at 4–5, ECF No. 104-20. Researchers documented the

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[47] Complement C4 is "a key molecule in the complement system that is one of chief constituents of innate immunity for immediate recognition and elimination of invading microbes . . . . Complement C4 is the most polymorphic protein in complement system. A plethora of research data demonstrated that individuals with C4 deficiency are prone to microbial infections and autoimmune disorders." H. Wang & M. Liu, *Complement C4, Infections, and Autoimmune Disease,* 12 FRONT IMMUNOL. 1–15 (2021).

[48] R. Brooks et al., *Prevalence of gastrointestinal, cardiovascular, autonomic and allergic manifestations in hospitalized patients with Ehlers-Danlos syndrome: a case-control study,* 60 RHEUMATOL. 4272–80 (2021).

[49] ABUL K. ABBAS et al., CELLULAR & MOLECULAR IMMUNOLOGY 1–11 (Elsevier eds., 9th ed. 2018).

[50] T. Lawley et al., *A Prospective Clinical and Immunologic Analysis of Patients with Serum Sickness,* 311:22 N. ENG. J. MED. 1407–14 (2011).

onset of clinical signs and symptoms within 2 weeks, but as early as 8 days. *Id.* at 2–3. This is consistent, according to Dr. Axelrod, with the onset of Petitioner's amenorrhea within a month of her second Gardasil injection. Pet'r's Ex. 126 at 21. Dr. Axelrod explained that "[d]epending upon the actual time interval between the vaccination and the onset of [Petitioner's] amenorrhea, this timing is consistent with a secondary adaptive immune response, or even a primary adaptive immune response, if she had not developed immune memory after the first Gardasil injection." *Id.* Dr. Axelrod concluded by noting that his theory accounts for her amenorrhea, POI, and POTS by way of HPV and flu vaccines. *Id.* at 22.

V. Respondent's Expert Reports[51]

A. Dr. Corrine Welt

Dr. Welt noted that Petitioner "had three normal FSH and estradiol levels in the [same] time frame [as her] documented irregular menses and amenorrhea." Resp't's Ex. M at 6. Based on these findings, she concluded that Petitioner does not meet "the classic definition" of "4–6 months of amenorrhea with elevated FSH in the menopausal range and low estradiol[]" to meet the diagnostic criteria for POI. *Id.*

Dr. Welt noted that Petitioner's "medical records document that [she] had menarche at age 13 years, but do not provide information about menstrual cycle regularity in contemporaneous doctor [sic] visits." *Id.* at 5. The irregularity of Petitioner's cycles from August of 2013 through November of 2014 appears in the record "by recall, and the mother state[d] that [P]etitioner had irregular menstrual cycles starting in [August of 2013], with amenorrhea starting [in October of 2013]." *Id.* (citing Pet'r's Ex. 3 at 89, 95, 108, 111). During this time, however, Dr. Welt noticed there was also weight loss documented in the medical record. *Id.* at 6. Dr. Welt reasoned that Petitioner's weight fluctuations could be the cause of her menstrual irregularity.[52] *Id.*

In his report, Dr. Axelrod offered the timing of the irregularity of Petitioner's cycles in relation to her second HPV vaccine in October of 2013 as evidence that she acquired POI post vaccination. *Id.* at 7 (citing Pet'r's Ex. 126). However, Dr. Welt noted that "documentation [i]n [August of 2013] indicate[d Petitioner's] cycles were already irregular by recall. Then, regular menstrual cycles were documented at medical visits after [February 17, 2015]." *Id.* Dr. Welt

[51] Respondent likewise filed expert reports in the eight consolidated cases in contemplation of *Althen* prong one from Drs. Thomas Forsthuber, David Frankfurter, and Robert Yokel. Those reports will not be recounted herein, though they may be referenced as necessary.

[52] Dr. Welt relied on several notations in the medical record that noted Petitioner's weight fluctuations. Resp't's Ex. M at 6. For instance, at menarche in 2013, Petitioner's weight was 141 lbs. On May 22, 2013, her height was listed as 5'7" and her weight was 143 lbs., making her BMI 22 kg/m2. *See id.* Dr. Welt then noted that there was a "dip in [Petitioner's] weight" between ages 16 and 17, when her menstrual irregularities began. Pet'r's Ex. 18 at 24–25. Specifically, her medical records note on January 27, 2014, that Petitioner had experienced a ten-pound weight loss, weighing 132 lbs., and her BMI was 20.5 kg/m2. Pet'r's Ex. 16 at 26. By May of 2014, Petitioner weighed 138 lbs. and her BMI was 21.4 kg/m2. Pet'r's Ex. 15 at 58. Dr. Welt noted that by the time her menstrual cycles returned to normal in 2015, Petitioner's weight was increasing. Resp't's Ex. M at 6. Petitioner weighed 159 lbs. on July 17, 2015, and 152 lbs. on August 5, 2015. *Id.* (citing Pet'r's Ex. 15 at 151, 172). Dr. Welt observed that Petitioner's menstrual cycles were present when her BMI was > 22 kg/m2. *Id.*

contended that Dr. Axelrod's assertions that "[Petitioner's] disorder was acquired[] and that she developed amenorrhea after her [second] Gardasil injection 'without resolution' are incorrect." *Id.*

Dr. Welt bolstered Dr. Axelrod's statement that "it is not clear that [Petitioner] suffered from [POI]." *Id.* Dr. Axelrod cited Dr. Olive's concerns that Petitioner's AMH levels in the lower end of the normal range meant she would progress toward POI, but Dr. Welt also noted Dr. Baker's conclusions that "healthy girls have AMH levels in the range of [P]etitioner[and] that [AMH] is not used for the diagnosis of POI." *Id.* Ultimately, Dr. Welt concluded that Petitioner's "transient irregular menses and amenorrhea approximately one year [post] vaccinations," were "coincident with weight loss." *Id.* at 8. She ruled out POI due to Petitioner's normal relevant hormone levels. *Id.* She opined that Petitioner's "autoimmunity profile is not needed in the absence of a POI diagnosis, but nonetheless there is no evidence of autoimmune POI." *Id.*

B. Dr. Thomas G. Forsthuber

Respondent filed a second report from Dr. Forsthuber that focused on the autoimmune etiology of Petitioner's condition. *See* Resp't's Ex. O. He began with a summary of Petitioner's medical records, including diagnoses pre and post vaccination, laboratory testing, ovarian functionality, and CellTrend assays. *Id.* at 1–7. Dr. Forsthuber acknowledged his "defer[ence] to the clinical expert Dr. Welt on [Petitioner's] diagnosis of POI," but he then noted that "[e]very antibody test for POI, adrenal, thyroid, or other autoimmune condition was negative." *Id.* at 10.

Dr. Forsthuber identified several points that Dr. Axelrod made in his reports for discussion. *See id.* He agreed with Dr. Axelrod's recount of Petitioner's labs and Dr. Axelrod's "acknowledg[ment] that her inflammatory markers (i.e.[,] [C-reactive protein]) were normal." *Id.* Dr. Forsthuber concluded that, "[t]aken together, Dr. Axelrod acknowledge[d] that [Petitioner] did not have laboratory[-]supported evidence of autoimmune POI or other autoimmune or inflammatory conditions." *Id.* at 11. Dr. Forsthuber addressed Dr. Axelrod's opinion that Petitioner suffered from complement activation, which "suggests an immune insult to her ovulatory physiology." *Id.* at 12. Dr. Forsthuber strongly disagreed with this assessment. *Id.* He noted that Petitioner's "complement of C4 was normal on [December 6, 2013,] (18 mg/dL; ref. range 15–57 mg/dL), and her complement C3 was minimally lower at 80 mg/dL (ref. range 83–193 mg/dL)." *Id.* Dr. Forsthuber again noted Petitioner's negative autoantibody testing, normal erythrocyte sedimentation rate ("ESR"),[53] and normal hormone levels in December of 2013. *Id.* He concluded that "there is absolutely no reliable evidence for POI and, even less so, for an 'immune insult' to [Petitioner's] ovaries." *Id.*

In response to Dr. Axelrod's reliance on AMH antibodies as evidence of autoimmune POI in Petitioner's case, Dr. Forsthuber first noted that he had been unable to find any articles that "have reported on the presence of autoantibodies against AMH or AMH receptors in POI/POF."

[53] ESR refers to "the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood, measured by the distance the top of the column of erythrocytes falls in a given time interval under specified conditions; an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins, which decrease the zeta potential on erythrocytes by dielectric shielding and thus promote rouleau formation. It is increased in monoclonal gammopathy, hypergammaglobulinemia due to inflammatory disease, hyperfibrinogenemia, active inflammatory disease, and anemia." *Dorland's* at 1594.

Id. at 13. He then explained that even if viable, Dr. Axelrod's theory is inapplicable to Petitioner's case "because [her] AMH levels [] did not correspond to her menstrual cycle irregularities." *Id.* For example, Petitioner's AMH levels tested throughout 2014, (in February (1.7 ng/ml), May (2.6 ng/ml), November (2.8 ng/ml), and December (1.8 ng/ml)), were all within the normal range of 0.9 to 9.5 ng/ml. *Id.* at 13–14. However, Dr. Forsthuber acknowledged that Petitioner reported breakthrough bleeding without menses and cycle irregularities in late summer and fall of 2014. *Id.* at 14.

Dr. Forsthuber also discussed the Komorowska article[54] and Dr. Axelrod's contention that in POI patients, "the follicular supply is exhausted, including the target antigen for the autoimmune attack on the ovary." *Id.* (citing Pet'r's Ex. 137). This, Dr. Forsthuber contended, is also inconsistent with Petitioner's presentation. *Id.* Petitioner's ultrasound, "on several occasions revealed ovarian follicles. Thus, there is no evidence that an autoimmune attack on the ovaries exhausted the follicular supply." *Id.* Dr. Forsthuber asserted that, as illustrated by Petitioner's clinical presentation, "Dr. Axelrod's own references disprove his claims." *Id.*

According to Dr. Forsthuber, Petitioner's March 17, 2022 antibody testing revealed positive results, but Petitioner "did not have evidence of any of the specific diseases associated with these autoantibodies." *Id.* at 15. Regarding Petitioner's EDS diagnosis, Drs. Axelrod and Forsthuber disagreed on the significance of this condition. *Id.* Dr. Axelrod noted a higher prevalence of autonomic dysfunction, specifically POTS, in patients with EDS and argued that this could be evidence of Petitioner's POTS diagnosis. *Id.* (citing Pet'r's Ex. 126 at 12). Dr. Forsthuber opined that because "EDS is not an autoimmune but a genetic condition," this diagnosis in Petitioner may be evidence of POTS with a non-autoimmune etiology. *Id.*

Like Dr. Axelrod, Dr. Forsthuber argued the merits of a molecular mimicry mechanism for vaccine-caused POI, despite my previous Ruling. *Id.* at 16. He acknowledged that "Dr. Shoenfeld's earlier-expressed causation theory has been accepted by the Court." *Id.* However, he also addressed "Dr. Axelrod's additional contentions." *Id.* Dr. Forsthuber wrote that "[t]here is no evidence that rare similarities of 3-amino acid peptides that [Dr. Axelrod] alleges with his [homology] searches induced immune responses after infection with viruses or bacteria, or in particular, after [the] HPV vaccination." *Id.* Dr. Forsthuber cited the Kanduc et al.[55] article as evidence that "suggests that peptide motif sharing is a constant property of the viral proteomes, exclusively depending on the viral proteome length and with no relationship to other structural and/or pathogenic viral features." Resp't's Ex. O, Tab 3 at 7, ECF No. 108-4. Likewise, the Trost et al.[56] article noted that "about 50,000 perfect sequences, each 9 amino acids long, are shared between the 40 bacterial proteomes described [therein] and about one third of the human proteome." Resp't's Ex. O, Tab 9 at 1, ECF No. 108-10. The article continued, "past and present data tend to exclude a causal mechanistic role for molecular mimicry in the genesis of autoimmunity." *Id.* at 3. The authors opined that "it is difficult to reconcile the enormous number of viral and bacterial peptides disseminated throughout the human proteins with a fundamental

[54] B. Komorowska, *Autoimmune premature ovarian failure,* 15(4) MENOPAUSE REV. 210–14 (2016).
[55] D. Kanduc et al., *Massive peptide sharing between viral and human proteomes,* 29 PEPTIDES 1755–66 (2008).
[56] B. Trost et al., *Bacterial peptides are intensively present throughout the human proteome,* 1:1 SELF/NONSELF 71–74 (2010).

role for molecular mimicry in the etiology of certain autoimmune conditions." *Id.* They alternatively proposed "that the high number of bacterial sequences that are also found in the human proteome, but are not clinically relevant in terms of inducing autoimmune diseases, offers a mechanistic basis for an additional microbial immune evasion strategy." *Id.*

Dr. Forsthuber concluded that the significant difference in length between two of the proteins Dr. Axelrod identified as potential mimics made it "extremely unlikely that processing of these proteins would generate exactly this region of 3 amino acids for the proteins that Dr. Axelrod claims as [a] 'molecular mimic.'" Resp't's Ex. O at 20. Likewise, Dr. Forsthuber argued that "it is highly unlikely that the sequences would line up exactly the same way in the MHC peptide-binding pocket and that T cells induced by the HPV L1 vaccine could induce [autoantibodies]." *Id.* Even in cases where similarity could be established, Dr. Forsthuber rebutted Dr. Axelrod's assertion that "amino acid similarity, not identity, is a predictive measure of crossreactivity [sic]." *Id.* The Frankild et al.[57] article that Dr. Axelrod cited in support of this contention is referenced by Dr. Forsthuber, who argued that "the authors show that the greater the similarity is between the viral epitopes and self-antigen epitopes, the less immunogenic these epitopes are." *Id.* (citing Pet'r's Ex. 146).

Dr. Forsthuber undertook a lengthy discussion[58] of Dr. Axelrod's "misconceptions about sequence alignments, [] fundamental mistakes in how to use [the sequencing search] program, and [] misinterpretation of his [search] results[.]" *See id.* at 21–26. He criticized Dr. Axelrod's misapplication of the search tool for use to compare only two proteins. *Id.* at 21. Dr. Forsthuber argued that Dr. Axelrod's conclusions are "unreliable." *Id.* at 26. He examined Dr. Axelrod's evidence and determined that Dr. Axelrod did not find amino acid sequences of 3–10 or 3–7 conserved similar amino acids as he claimed. *Id.* at 22 (citing Pet'r's Exs. 151–64, ECF Nos. 104-24–104-37). "By [Dr. Forsthuber's] count, for all except HPV18[, Dr. Axelrod] f[ound] only one region across the entire protein where three amino acids [] overlap[.]" *Id.* He therefore maintained that Dr. Axelrod's clustal searches and alleged sequence similarities are "meaningless" and do not provide evidence of molecular mimicry in Petitioner's case or in POI in general. *Id.* at 26.

C. Dr. Amy Arnold

Dr. Arnold's report "focus[ed] on the POTS pathophysiology and diagnosis" and ultimately concluded that "while it is clear [P]etitioner has experienced a constellation of symptoms, both before and after her HPV vaccinations, she does not meet the diagnostic criteria

[57] S. Frankild et al., *Amino Acid Similarity Accounts for T Cell Cross-Reactivity and for "Holes" in the T Cell Repertoire,* 3(3) PLoS ONE 1831–39 (2008).

[58] Throughout this discussion, Dr. Forsthuber attacked Dr. Axelrod's accepted sequence length reflective of a molecular mimic. Resp't's Ex. O at 16. He cited medical literature attempting to refute that a short chain of five to nine homologous amino acids is not sufficient to show molecular mimicry. *Id.* (citing Resp't's Ex. O, Tab 3; Resp't's Ex. O, Tab 9). Rather, he argued that the optimal length of a peptide for binding to major histocompatibility complex molecules is "approximately 18–20 amino acids." *Id.* at 19 (citing Resp't's Ex. O, Tab 7, ECF No. 108-8). Dr. Forsthuber argued that Dr. Axelrod's alleged HPV molecular mimic of 3 amino acids is "dramatically shorter" than the optimal length. *Id.* at 19–20. Dr. Forsthuber also took issue with Dr. Shoenfeld's proposed 5-amino acid sequence homologies. *Id.* at 19. However, after careful consideration, I have already credited Petitioner's proposed minimum sequence length of 5 amino acids in my Ruling on *Althen* prong one. *See Brayboy,* 2021 WL 4453146, at *1.

for POTS." Resp't's Ex. P at 6. Dr. Arnold described POTS as "a heterogenous clinical disorder that is characterized by excessive increases in heart rate upon standing, in the absence of low blood pressure, and with chronic symptoms of orthostatic intolerance that are relieved by lying down." *Id.* (citing Resp't's Ex. P, Tab 2, ECF No. 110-3; Resp't's Ex. P, Tab 16, ECF No. 110-17).[59] She identified current consensus diagnostic criteria, including sustained heart rate increases, symptoms of orthostatic intolerance, absence of orthostatic hypotension, and absence of overt causes for sinus tachycardia.[60] *Id.* (citing Resp't's Ex. P, Tab 2 at 2). Dr. Arnold noted Petitioner's post-vaccination reports as follows:

Report	**Date of Complaint**	**Cite**
Decreased blood pressure	January 2014	Pet'r's Ex. 2a at 12
Decreased heart rate	April 2014	Pet'r's Ex. 3b at 115
Echocardiograms (normal)	August 2014 January 2016 November 2016 August 2017	Pet'r's Ex. 121 at 39, 103, 164, 261
Home-based monitoring (normal)	April 2014 August 2018 October 2018	Pet'r's Ex. 3 at 389 Pet'r's Ex. 121 at 391 Pet'r's Ex. 119 at 12
EKGs with low and high heart rate	November 2016 September 2017 June 2019	Pet'r's Ex. 121 at 165, 262, 544

According to Dr. Arnold, these are all inconsistent with a POTS diagnosis. Resp't's Ex. P at 6.

Furthermore, Dr. Arnold asserted that Petitioner's "autonomic function tests and orthostatic vital signs were normal post vaccination and showed no evidence of autonomic issues, including POTS."[61] *Id.* at 7. In support of her assessment, Dr. Arnold cited a record of autonomic testing done by Dr. G. Chelimsky on August 14, 2017, which showed "no evidence of POTS." *Id.* (citing Pet'r's Ex. 119 at 27).

While acknowledging suggestions in the medical community that POTS may have an autoimmune phenotype, Dr. Arnold opined that "current scientific evidence [] does not establish the likelihood that autoimmunity is actually involved in the pathophysiology of POTS." *Id.* at 8. Studies on the presence of autoantibodies to diagnose POTS have been inconsistent, with some finding elevated antibodies against adrenergic receptors, and some finding no difference between

[59] A. Arnold et al., *Postural tachycardia syndrome – Diagnosis, physiology, and prognosis,* 215 AUTONOM. NEUROSC. 3–11 (2018); R. Sheldon et al., *2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope,* 12:6 HEART RHYTHM 41–64 (2015).

[60] Sinus tachycardia is the "excessive rapidity in the action of the heart (in the sinus node); the term is usually applied to a heart rate above 100 beats per minute in an adult[.]" *Dorland's* at 1867.

[61] Dr. Arnold notes "[t]he only occasion on which [P]etitioner actually met heart rate criteria for POTS was in August [of] 2018, about five years after her HPV vaccinations, and shortly after she was reported to suffer from an ischemic stroke event." Resp't's Ex. P at 7. Petitioner's vital signs returned to normal range when measured during a follow-up visit, approximately six months later. *Id.*

autoantibody concentrations in diagnosed patients and healthy controls. *Id.* Dr. Arnold quoted the Miglis et al.[62] article in support: "adrenergic, muscarinic[,] and angiotensin receptor antibodies have not been proven to be causative or useful in confirming a diagnosis of POTS." *Id.* (citing Resp't's Ex. P, Tab 12 at 1, ECF No. 110-13). The article questioned if "these autoantibodies, which seem ubiquitous in the serum of POTS patients, [are] a mechanistic cause of disease or rather a bystander effect of the disease process." Resp't's Ex. P, Tab 12 at 1. The authors also questioned, "[i]f the autoantibodies are causative, should we expect evidence of autonomic failure due to tissue destruction at some point in the natural history of POTS, as we see in autoimmune autonomic ganglionopathy?" *Id.* at 2. Miglis et al. concluded that "at this time, [such antibodies] have not been proven to be causative or useful in confirming a diagnosis of POTS." *Id.* at 3.

POTS is Dr. Arnold's area of expertise, but she noted "there is no evidence supporting a connection between POTS and POI." Resp't's Ex. P at 8. She could not find a study that suggested such an association. *See id.* However, she cited the Peggs et al.[63] study of gynecologic disorders in POTS patients, which noted the potential for the patients' recall bias for other symptoms. *Id.* (citing Resp't's Ex. P, Tab 13 at 6, ECF No. 110-14). For example, POTS patients reported on a questionnaire, symptoms including increased lightheadedness during the menstrual cycle, a higher incidence of secondary amenorrhea, and a higher incidence of gynecologic abnormalities, but none of the patients had POI. *See* Resp't's Ex. P, Tab 13 at 6.

Petitioner's EDS diagnosis is not disputed by any of the experts, and Dr. Arnold hypothesized that "the constellation of symptoms described throughout [P]etitioner's medical records are consistent with hypermobile [EDS]." Resp't's Ex. P at 9. This assertion is consistent with Dr. T. Chelimsky's statement that "[EDS] probably contributes to POTS[,]" referring to both Petitioner's POTS and POTS in general. *Id.* at 10 (citing Pet'r's Ex. 122 at 16). Dr. Arnold also cited Petitioner's genetic counselor who, considering Petitioner's "complex health history and maternal family history of similar features," believed many of Petitioner's "symptoms clinically overlap with hypermobile [EDS]." *Id.* (citing Pet'r's Ex. 121 at 824). Dr. Arnold noted that EDS is a hereditary connective tissue disorder that "can also be accompanied by cardiovascular complications such as low blood pressure, vasovagal syncope, and orthostatic intolerance, including POTS." *Id.* at 9 (citing Resp't's Ex. P, Tab 8, ECF No. 110-9).[64] She wrote that causes for this comorbidity include, abnormal blood vessel physiology, "neuropathy, connective tissue laxity, adrenergic receptor hyper-responsiveness, and the use of vasoactive medications." *Id.*

Dr. Arnold identified several large-scale assessments of an increased incidence of POTS following the HPV vaccine when compared to unvaccinated adolescents. *Id.* at 10–11 (citing Resp't's Exs. P, Tabs 1, 3, 5, 14, ECF Nos. 110-2, 110-4, 110-6, 110-15).[65] None of these authors

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[62] M. Miglis et al., *Is postural tachycardia syndrome an autoimmune disorder? And other updates on recent autonomic research,* 30 CLIN. AUTONOM. RES. 3–5 (2020).

[63] K. Peggs et al., *Gynecologic disorders and menstrual cycle lightheadedness in postural tachycardia syndrome,* 118(3) INT. J. GYNECOL. OBSTET. 242–46 (2013).

[64] A. Hakim et al., *Cardiovascular Autonomic Dysfunction in Ehlers-Danlos Syndrome – Hypermobile Type,* 175C AM. J. MED. GEN. 168–74 (2017).

[65] J. Arana et al., *Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System,* 61 J. ADOLESC. HEALTH 577–82 (2017); A.

found a higher incidence of POTS in adolescents who had received the HPV vaccination. *See id.* The American Autonomic Society went further and asserted that the identified studies offering a dissenting opinion only show weak temporal associations, and "the small sample sizes, inherent selection biases, and lack of control populations preclude drawing any scientifically valid conclusions of causality." *See* Resp't's Ex. P, Tab 3 at 3.

There were several of Dr. Axelrod's contentions that Dr. Arnold responded to directly in her report. Resp't's Ex. P at 12. Dr. Arnold attacked Dr. Axelrod's reliance on Petitioner's treater's notations regarding POTS. *Id.* She questioned why, after finding Petitioner did not meet the diagnostic criteria for POTS on May 12, 2014, Dr. G. Chelimsky reversed course after re-evaluation on August 4, 2014, and diagnosed Petitioner with POTS. *Id.* Dr. Arnold opined there was "no basis for [Dr. G. Chelimsky's] change in diagnosis, as [Petitioner's] orthostatic vitals taken during standing at re-evaluation . . . still showed that heart rate changes did not meet diagnostic criteria for POTS at this visit." *Id.* In support of her opinion, Dr. Arnold referenced Petitioner's cardiologist Dr. McDonnell, who "indicated in 2016 that, '[h]er current episodes are not consistent with POTS. There is not a postural component.'" *Id.* (citing Pet'r's Ex. 121 at 40).

Dr. Arnold also questioned the relevance of Dr. Axelrod's identification of "two shared sequences between HPV strains and fibroblast growth factor receptor 3," because Petitioner "had negative results for anti-fibroblast growth factor receptor 3 antibodies in 2018 and 2022." *Id.* (citing Pet'r's Exs. 114–15).

Lastly, Dr. Arnold took issue with the proximate temporal relationship between the vaccination and the injury as outlined by Dr. Axelrod. *Id.* at 13. Dr. Arnold noted that Petitioner's "cardiovascular-related symptoms were already present prior to vaccination," and "all reports immediately following vaccination suggested . . . decreased blood pressure and heart rate . . . , which is not consistent with the increase in heart rate upon standing that clinically defines POTS." *Id.*

VI. Applicable Law

I am resolving Petitioner's claim on the filed record. The Vaccine Act and Rules not only contemplate but encourage special masters to decide petitions on the papers where, in the exercise of their discretion, they conclude that doing so will properly and fairly resolve the case. *See* 42 U.S.C. § 12(d)(2)(D); Vaccine Rule 8(d). The decision to rule on the record in lieu of hearing has been affirmed on appeal. *Kreizenbeck v. Sec'y of Health & Hum. Servs.*, 945 F.3d 1362, 1366 (Fed. Cir. 2020); *see also Hooker v. Sec'y of Health & Hum. Servs.*, No. 02-472V, 2016 WL 3456435, at *21 n.19 (Fed. Cl. Spec. Mstr. May 19, 2016) (citing numerous cases where special masters decided cases on the papers in lieu of hearing and those decisions were upheld). I am simply not required to hold a hearing in every case, no matter the preferences of the parties. *Hovey v. Sec'y of Health & Hum. Servs.*, 38 Fed. Cl. 397, 402–03 (1997) (determining that the special master acted

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Barboi et al., *Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society,* 223 AUTONOM. NEUROSC. 1–5 (2020); B. Butts et al., *Human Papillomavirus Vaccine and Postural Orthostatic Tachycardia Syndrome: A Review of Current Literature,* X J. CHILD NEUROL. 1–10 (2017); A. Phillips et al., *Safety of Human Papillomavirus Vaccines: An Updated Review,* 41 DRUG SAF. 329–46 (2018).

within his discretion in denying an evidentiary hearing); *Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993); *Murphy v. Sec'y of Health & Hum. Servs.*, No. 90-882V, 1991 WL 71500, at *2 (Fed. Cl. Spec. Mstr. Apr. 19, 1991).

To receive compensation under the Vaccine Act, a petitioner must demonstrate either that: (1) the petitioner suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) the petitioner suffered an "off-Table injury," one not listed on the Table, as a result of his receiving a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioner does not allege a Table injury in this case; thus, she must prove that her injury was caused-in-fact by a Table vaccine.

It is each petitioner's burden to demonstrate by a preponderant standard that the subject of the claim actually suffers from the injury alleged to have been caused by the identified vaccination(s). *See Hibbard v. Sec'y of Health & Hum. Servs.*, 698 F.3d 1358, 1364–65 (Fed. Cir. 2012); *Lombardi v. Sec'y of Health & Hum. Servs.*, 656 F.3d 1343, 1353 (Fed. Cir. 2011); *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). Petitioner's diagnoses are in dispute not only between the parties, but also between Petitioner's treaters and her own experts. Although the various conditions asserted by medical professionals in this case may "present with many of the same symptoms, their underlying causes are different and require different treatments." *See Broekelschen,* 618 F.3d at 1344. To decide if Petitioner is entitled to damages, "it [i]s appropriate in this case–where virtually all of the evidence on causation [i]s dependent on the diagnosis [and etiology of Petitioner's] condition–for [me] to determine the proper diagnosis before applying the *Althen* test." *Id.*; *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278–79 (Fed. Cir. 2005).

In the seminal case of *Althen*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d at 1278–79. The *Althen* test requires petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Each *Althen* prong requires a different showing. Under the first prong, a 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 & Hum. Servs.,* No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352, 1355–56 (Fed. Cir. 2006). To satisfy this prong, a petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). This theory need only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548. Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

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. In Program cases, contemporaneous medical records and the opinions of treating physicians are favored. *Capizzano,* 440 F.3d at 1319–20 (citing *Althen*, 418 F.3d at 1280). This is because "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.'" *Id.* In addition, "[m]edical records, in general, warrant consideration as trustworthy evidence . . . [and] are generally contemporaneous to the medical events." *Cucuras v. Sec'y of Health & Hum. Servs.,* 993 F.2d 1525, 1528 (Fed. Cir. 1993). However, there is no presumption that medical records are accurate and complete as to all the patient's physical conditions. *Kirby v. Sec'y of Health & Hum. Servs.,* 997 F.3d 1378, 1383 (Fed. Cir. 2021). While a special master must consider these opinions and records, they are not "binding on the special master or court." 42 U.S.C. § 300aa-13(b)(1). Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ." *Id.*

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 & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *de Bazan,* 539 F.3d at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. 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).

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Hum. Servs*., 98 Fed. Cl. 719, 726 (2011). When and if a petitioner establishes a prima facie case, the burden then shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *de Bazan*, 539 F.3d at 1354; *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that the respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2).

VII. Analysis

A. Expert Reports

My August 30, 2021 Ruling was based on the proposed biological mechanism and the expert reports submitted up to that time. *See generally* Findings of Fact; *Brayboy,* 2021 WL 4453146. I found that "[the POI p]etitioners have articulated a sound and reliable theory of how HPV vaccines could cause autoimmune POI via molecular mimicry" and met their burden with

respect to *Althen* prong one. *See* Findings of Fact. More specifically, the POI petitioners' experts described "how autoantibodies can attack multiple short peptide chains contained within proteins needed for normal ovarian function, when said peptides are also contained within viral proteins identified by the immune system for destruction." *Id.* at 2. Pursuant to my Ruling, in order for this theory to be applicable to any individual POI petitioner for *Althen* prong two analysis, she must be able to establish by preponderant evidence that she suffers from autoimmune POI. I indicated that an autoimmune etiology will not be presumed for any claim and will be determined by each POI petitioner's individual medical history. I found that "[a] petitioner whose condition does not present evidence of an autoimmune etiology, such as lymphocytic oophoritis, adrenal or ovarian autoantibodies, and comorbid autoimmune disorders"[66] will likely be unable to establish the applicability of the theory. *Id.* at 24. I further cautioned that "[t]here should be autoimmune indicators in the medical record and not simply arguments from experts that despite a lack of direct support in the medical record, the claim should proceed because an autoimmune etiology cannot be definitively ruled out." *Id.*

In the present case, Petitioner's latest expert presents evidence that both deviates from the causation theory originally presented and contravenes my instruction that the "[p]etitioners should proceed with the prosecution of claims in accordance with [my August 30, 2021] Ruling." *See id.* Dr. Axelrod attempted to mitigate this noncompliance by noting that he "support[s] the molecular mimicry theory outlined therein by Dr. Shoenfeld." Pet'r's Ex. 126 at 13. However, Dr. Axelrod's extensive explanation of molecular mimicry is a direct violation of not only my August 30, 2021 Ruling, but also my December 14, 2021 Order, that any subsequent expert reports should address *Althen* prongs two and three. Findings of Fact; ECF No. 88 at 1. Dr. Axelrod identified several additional short peptide chains found within the various strains of HPV that are included in the Gardasil vaccine. *See* Pet'r's Ex. 126 at 13–16. He then asserted their relevance in a potential pathological molecular mimicry process, causing POI. Notably, he spent much of this section of his report discussing the mechanics of molecular mimicry generally and in the context of a tetanus, diphtheria, and/or pertussis infection. *See id.* at 14. Given the nature of the Program and the specific procedural history of this case, Dr. Axelrod's foundational discussion of molecular mimicry, with references to the Kanduc and Trost studies, was as unhelpful as it was unnecessary. *Id.* at 13 (citing Pet'r's Exs. 140–41). Further explanation by way of an analogy to tetanus, diphtheria, and/or pertussis was likewise ineffectual.

In the context of Petitioner's vaccinations and their relationship to POI, Dr. Axelrod listed a string of seven or eight proteins in the flu and HPV vaccines that contain three amino acids also found in AMH. *Id.* at 15. He then devoted a significant part of his report to AMH and its role in reproductive development. AMH levels are used in evaluating ovarian reserve for IVF. *See* Pet'r's Ex. 129 at 1. However, that AMH levels may be undetectable in POI patients does not make AMH levels a predictor of POI. Dr. Axelrod presented no medical literature to support such a conclusion. He referenced a study by Xu et al. on "the effect of blocking antibody to [AMH] upon granulosa cells and ovarian follicles." Pet'r's Ex. 126 at 9 (citing Pet'r's Ex. 132). He then opined that Petitioner "has circulating lymphocytes with specificity to [AMH that] upon exposure to the components of the Gardasil [vaccine], [were activated] with the production of antibodies to her [AMH]." *Id.* Petitioner's medical record did not indicate the presence of AMH antibodies, nor did

[66] Diseases, including autoimmune polyendocrine syndromes and Addison's disease, were identified by Respondent's expert Dr. Forsthuber, as effective predictors of autoimmune POI. Findings of Fact at 11.

her treaters note such antibodies during the entirety of Petitioner's POI testing. Dr. Axelrod asserted that this process further "resulted in the loss of early growing follicles and the loss of her ability to ovulate and have normal menses." *Id.* This assertion is contrary to the results of Petitioner's February 10, 2014 ultrasound, which revealed multiple follicles within both ovaries. Pet'r's Ex. 3b at 144.

Through his focus on AMH, Dr. Axelrod attempted to identify a potential, additional point of cross-reaction, but he did not submit persuasive evidence that it is more likely to occur than Dr. Shoenfeld's originally named proteins, or that it is likely to occur at all. He did not provide any literature or other evidence that specifically links molecular mimicry, vaccines, or autoimmune POI to AMH autoantibodies. While medical literature is not required, Dr. Axelrod offers only speculation, without any supporting evidence, of any causal association between AMH antibodies and POI. Indeed, the Moolhuijsen et al. study that Petitioner filed to discuss the role of AMH in reproductive health, noted that "recent studies suggest that the relationship between autoimmune diseases and diminished [functional ovarian reserve], as assessed by AMH, remains inconsistent." Pet'r's Ex. 130 at 9. The authors added that "well-controlled studies are needed to analyze the impact of disease onset, duration, and therapy on AMH levels." *Id.* Petitioner had already submitted a valid causation theory that explains the cross reaction "between L1 proteins contained in Gardasil and proteins essential to proper ovarian function." Findings of Fact at 19. This theory involves "an enzyme that helps a cell repair DNA damage" and "has been associated with the development of POI." *Id.* at 20–21. Although I specifically instructed Petitioner not to relitigate the viability of a biological mechanism for vaccine-induced POI, she filed an expert report that reiterates previously made points without additional preponderant evidence.

Dr. Axelrod also noted "a protective immune reaction to [Petitioner's] influenza vaccination," but he did not explain how the flu vaccine fits within the previously asserted theory or his new theory. The biological mechanism that was previously litigated for use in this case does not contemplate a flu vaccine. I will not allow Petitioner to make substantial, but ineffectual, changes to her argument six years into litigation, in an attempt to address facts that existed at the time her claim was filed. Frankly, Dr. Axelrod's vague mention of a flu vaccine is insufficient to explain how this additional immune system trigger would change the molecular mimicry mechanism already presented.

Lastly, Dr. Axelrod added that Petitioner has "a condition, [EDS], that deserve[s] further comment and analysis." Pet'r's Ex. 126 at 13. The case consolidation that includes Petitioner's claim was premised on the shared, identified injury of POI. EDS is a condition that *Dorland's* defines as "a group of inherited disorders of connective tissue."[67] EDS is not an autoimmune condition, nor is it associated with POI. Dr. Axelrod does not claim as much. Like his mention of Petitioner's flu vaccine, it is unclear how this diagnosis affects any claim of HPV vaccine-caused POI. Dr. Axelrod's recent additions to Petitioner's biological mechanism do not amount to preponderant evidence applicable to *Althen* prongs one, two, or three.

Respondent's expert Dr. Forsthuber also devoted a significant portion of his most recent expert report to renewed objections to the molecular mimicry causation theory. *See* Resp't's Ex. O. He, like Dr. Axelrod, noted an "understanding that Dr. Shoenfeld's earlier-expressed causation

[67] *See supra,* note 16 (defining Ehlers-Danlos Syndrome).

theory has been accepted by the Court." *Id.* at 16. Nevertheless, Dr. Forsthuber felt it necessary to rebut Dr. Axelrod's new evidence and asserted that "this massive amount of sequence sharing of peptides between proteins from bacteria/viruses and humans does not support their role in human disease processes via molecular mimicry." *Id.* As I did not find Dr. Axelrod's newly submitted evidence in support of molecular mimicry probative, I will not spend additional time addressing Respondent's rebuttal. Such arguments are untimely and, to a degree, moot. As explained below, Petitioner is unable to establish that she has the injury alleged or that her vaccinations resulted in an autoimmune pathogenic process. Therefore, the theory proposed, and any additional supporting or refuting evidence with respect to *Althen* prong one, is of no further consequence in this case.

B. POI Diagnosis

Before deciding whether the evidence supports an autoimmune etiology for Petitioner's condition, I must first assess the evidence of her diagnosis. *See Broekelschen,* 618 F.3d at 1344 ("[I]t [i]s appropriate in this case–where virtually all of the evidence on causation [i]s dependent on the diagnosis [and etiology of a petitioner's] condition–for [the special master] to determine the proper diagnosis before applying the *Althen* test."). *Dorland's* defines POI as the "absence or irregularity of menses lasting at least four months, with menopausal levels of serum gonadotropins, in an adolescent girl or woman under 40 years of age."[68] In my August 30, 2021 Ruling, I relied on the filed medical literature and expert consensus and defined POI as amenorrhea lasting for more than four months in a woman younger than 40 years of age. *See* Findings of Fact at 9–10; *Brayboy,* 2021 WL 4453146, at *7. The amenorrhea must be accompanied by FSH levels greater than 40 IU/mL on two occasions. *See* Findings of Fact at 9–10. I also noted that clinical symptoms such as hot flashes and night sweats, sleep disturbances, and dyspareunia[69] may be supportive evidence. *Id.*

Petitioner's expert questioned whether Petitioner actually suffered from POI. Dr. Axelrod detailed Petitioner's normal laboratory results following her HPV vaccinations and noted that "[s]he did not suffer from hot flashes, night sweats, excessive sweating or hair loss." Pet'r's Ex. 126 at 11. Indeed, Petitioner's FSH levels tested normal on January 13, 2014, February 1, 2014, June 1, 2015, and as recently as September 21, 2022. Pet'r's Ex. 7 at 7, 16, 26; Pet'r's Ex. 120 at 6, ECF No. 102-5. Dr. Axelrod then stated, "it is not clear that she suffered from [POI]." Pet'r's Ex. 126 at 11. His plain application of the diagnostic criteria to Petitioner's medical record does not support a finding by a preponderant standard that Petitioner developed POI.

Dr. Axelrod is not a reproductive specialist, however. In support of his argument that Petitioner developed POI, Dr. Axelrod referenced a July 14, 2015 medical record, signed by Dr. Minjarez from the Colorado Center for Reproductive Medicine, that stated Petitioner had progressed to POI. Pet'r's Ex. 16 at 20. The record listed POI as an assessment but noted that Petitioner's 2013 AMH levels had improved over the last two years with "resumption of her regular cycles." *Id.* at 21. The record continued that Petitioner "ha[d] been evaluated by neurology, rheumatology, and hematology with no definitive diagnosis." *Id.* Dr. Minjarez wrote that as of June 11, 2015, Petitioner's "cycles ha[d] returned regularly, every 26–27 days." *Id.* at 25. Dr. Minjarez did not identify medical records that document amenorrhea, accompanied by increased

[68] *See supra,* note 4 (defining POI).
[69] Dyspareunia is "difficult or painful sexual intercourse." *Dorland's* at 579.

FSH levels, to support this POI assessment. Dr. Axelrod, likewise, did not cite to a clinical presentation of symptoms in Petitioner's medical record that further supports Dr. Minjarez's POI diagnosis.

Dr. Gersh is Petitioner's reproductive expert, and she also noted that Petitioner's medical record "indicated the development of [POI]." Pet'r's Ex. 23 at 1. In her brief report, Dr. Gersh admitted that Petitioner's FSH levels remained normal, but Dr. Gersh instead relied on Petitioner's fluctuating estrogen levels, a low antral follicle count, and "most importantly," low AMH levels to support a POI diagnosis. Dr. Gersh did not explain the significance of a low antral follicle count or AMH levels in the context of a patient with normal FSH levels, to diagnose POI. She did not cite to or provide any medical literature that includes low AMH levels as part of the diagnostic criteria for POI. Dr. Gersh then hypothesized that Petitioner's prematurity caused her "poorly developed intestinal microbiome" to react somehow to the HPV vaccine and lead to the manifestation of POI. *Id.* She similarly did not cite to or provide any medical literature that explains how the intestinal microbiome is related to POI. She did not include in her report a logical sequence of cause and effect from the HPV vaccine to an intestinal immune reaction that culminates in the development of POI.

I must also note that despite Dr. Gersh's expertise in reproductive health, she does not identify POI as an area of specialty. Furthermore, her curriculum vitae does not list any training, experience, or expertise in prematurity complications or intestinal conditions. *See generally* Pet'r's Ex. 22. Without additional context from her or support in the medical literature, Dr. Gersh's opinion is conclusory and insufficient to meet the preponderant standard. Indeed, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Hum. Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. App'x. 999 (Fed. Cir. 2013).

Furthermore, I find it notable that Petitioner's initial POI diagnosis in December of 2013 was made via phone consultation in contemplation of egg preservation. Pet'r's Ex. 16 at 28. This diagnosis was not supported by any follow up lab reports or testing. The aggregate of: (1) Dr. Minjarez's assessment unsupported by diagnostics; (2) Dr. Axelrod's concurrence despite contradictory analysis; and (3) Dr. Gersh's conclusion short of explanation does not meet the preponderant standard for establishing diagnosis when each opinion is carefully examined.

Alternatively, Respondent's expert Dr. Welt is a reproductive specialist with experience researching, diagnosing, and treating POI. In her report, she evaluated Petitioner's medical record, focusing specifically on the patterns of amenorrhea and hormone levels. Dr. Welt showed that, while Petitioner did have some abnormal testing and amenorrhea, her records do not reflect amenorrhea coupled with the menopausal levels of serum gonadotropins needed to diagnose POI. Dr. Welt also noted that Petitioner did not suffer the clinical symptoms of menopause that are commonly seen in POI patients. She agreed with Dr. Axelrod's reading of Petitioner's medical record, which did not reveal POI symptoms, and remained unequivocal in her opinion. Dr. Welt concluded that Petitioner's condition did not meet the clinical or diagnostic criteria for POI.

After a consideration of the medical record, Petitioner has not presented preponderant evidence that she suffered from POI. Her symptoms are not consistent with the clinical presentation, and her hormone levels were not in the appropriate range at the time of her amenorrhea. Further, Petitioner did not present persuasive evidence that AMH levels are, or should be, used as a diagnostic factor for POI. She also did not present persuasive evidence that an irregular intestinal microbiome is relevant to the development of POI. Because Petitioner is unable to establish it more likely than not that she had POI, she cannot establish it more likely than not that she suffered from POI that is autoimmune in origin and caused by her vaccinations. Nonetheless, I will address the parties' arguments regarding autoimmune etiology.

C. Autoimmune POI

a. *Althen* Prong Two

Although Petitioner has not presented preponderant evidence that she suffered from POI, some of Petitioner's treaters noted "post[-]HPV amenorrhea." Pet'r's Ex. 3a at 99. While Dr. Kriege was one of those treaters, she "emphasize[d]" her lack of expertise in autoimmune reproductive issues. *Id.* As noted above, in Program cases, the opinions of treating physicians are favored and must be considered. *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). However, while a special master must consider these opinions and records, they are not "binding on the special master or court[,]" and I must consider the entire record. 42 U.S.C. § 300aa-13(b)(1).

Indeed, as a result of the suspicions of some of her treaters, Petitioner was routinely tested for evidence of autoimmune disease, generally, and autoimmune POI, specifically. Petitioner's most recently filed medical literature echoed her previously filed articles that articulate the evidence for an autoimmune etiology in POI patients. The Komorowska article identified "the presence of lymphocytic oophoritis, association with other autoimmune disorders, and autoantibodies to ovarian antigen" as factors "clearly documented in numerous studies." Pet'r's Ex. 137 at 2. I enumerated these same factors in my August 30, 2021 Ruling, and accordingly, will apply them to Petitioner's medical history to determine if she has presented preponderant evidence of autoimmune POI. *See* Findings of Fact at 24.

The Jankowska article filed by Petitioner, discussed POI caused by "an autoimmune process consisting of the production of anti-ovarian antibodies." Pet'r's Ex. 135 at 3. The Kirshenbaum et al. article, also filed by Petitioner, acknowledged that "[w]hile a specific noninvasive reliable diagnostic test for the diagnosis of an autoimmune etiology is lacking, nowadays, patients should be screened for the most common autoantibodies." Pet'r's Ex. 136 at 5. Dr. Axelrod conceded that Petitioner "did not have detectable anti-ovarian antibod[ies]," but he immediately asserted that "the presence or absence of this antibody does not prove or disprove an autoimmune cause for [POI]." Pet'r's Ex. 126 at 11. Despite his equivocation on Petitioner's diagnosis and Petitioner's lack of anti-ovarian antibodies, Dr. Axelrod ultimately identified her "low complement C3 level" and "detectable levels of antibodies, [including] to anti-adrenergic receptor antibodies and anti-muscarinic cholinergic receptor antibodies" in testing done on June 29, 2018, and March 14, 2022, as evidence of her autoimmune POI. *Id.* at 5. Petitioner received her HPV vaccines on July 22, 2013, and October 23, 2013. Pet. at 1. She underwent antibody testing on November 23, 2013 (Pet'r's Ex. 3a at 91), December 7, 2013 (Pet'r's Ex. 3c at 83),

August 26, 2014 (Pet'r's Ex. 3b at 143), June 1, 2015 (Pet'r's Ex. 2d at 36), and January 4, 2016 (Pet'r's Ex. 6 at 1). The June 1, 2015 record noted, "all antibody labs have returned negative (including anti-ovarian), which [sic] exception of mildly elevated ANA (very nonspecific)." Pet'r's Ex. 2d at 36. The 2016 labs were likewise negative. Pet'r's Ex. 6 at 1.

Dr. Axelrod placed a premium on Petitioner's positive test results beginning in 2018. He did not explain the negative results over the several years following vaccination, even when Petitioner's negative results continued after POI was initially suspected as early as December of 2013. For example, Dr. Kriege diagnosed Petitioner with post-HPV amenorrhea in January of 2014, but she wrote there were no signs on exam or on lab of a systemic autoimmune disease. Pet'r's Ex. 3a at 99. She reiterated that position in May of 2015, despite Petitioner's low AMH levels, and noted that Petitioner's post-HPV amenorrhea was improving. *Id.* at 168. Dr. Seroogy noted in February of 2014 that Petitioner had "no clinical or laboratory evidence of autoimmune-mediated ovarian failure or other autoimmune endocrine problems." Pet'r's Ex. 15 at 30.

In light of such notations, Dr. Axelrod's reliance on positive test results obtained in 2018 and 2022 is tenuous, if not irrelevant, to Petitioner's vaccinations received approximately five years prior. The weight of the evidence is further lessened by interim, negative tests, despite the alleged progression of Petitioner's POI during that time. Furthermore, Petitioner tested positive for antibodies in 2018. However, based on lab work on March 14, 2022, Petitioner had normal AMH, FSH, LH, and estradiol levels, with a good egg retrieval score. Pet'r's Ex. 125 at 1. This is wholly inconsistent with a POI diagnosis, with or without an autoimmune etiology. Petitioner's comprehensive antibody testing therefore does not provide preponderant evidence of an autoimmune etiology.

Dr. Axelrod further noted that Petitioner did not develop adrenal insufficiency, diabetes, or thyroiditis. Pet'r's Ex. 126 at 12. Indeed, he did not suggest that Petitioner suffered from any autoimmune comorbidity. He stated only that she is at "risk for the development of an autoimmune disorder." *Id.* Given the amount of time that has elapsed since her vaccination, the failure of any such disorder to manifest nullifies the probative value of Dr. Axelrod's purported risk. While Petitioner's medical record documents an extensive history of adverse vaccine reactions and rashes, these manifestations were similar in their locality and acute onset, unlike autoimmune polyendocrine syndromes,[70] Addison's disease,[71] or other autoimmune conditions that are chronic in nature and associated or comorbid with POI. *See* Findings of Fact at 24. In fact, Petitioner's medical record dated May 29, 2015, noted that no autoimmune diagnosis had been made to date. Pet'r's Ex. 2c at 36. Petitioner did not suffer from any comorbid autoimmune disease that could provide preponderant evidence of autoimmune POI. Lastly, it is undisputed that Petitioner did not exhibit any signs of lymphocytic oophoritis.

After a thorough examination of Petitioner's medical record, Petitioner has not presented preponderant evidence that any of the enumerated factors used to identify autoimmune POI are

[70] Autoimmune polyendocrine syndromes, or polyendocrine autoimmune syndromes, are "syndromes comprising combinations of endocrine and nonendocrine autoimmune diseases." *Dorland's* at 1844. It is characterized by the presence of two of three major clinical symptoms: candidiasis, hypoparathyroidism, and adrenal insufficiency. *Id.*

[71] *See supra,* note 15 (defining Addison's disease).

present in her case. Therefore, the causation theory based on molecular mimicry presented by Dr. Shoenfeld and credited in my Ruling, is inapplicable. Petitioner has failed to meet her burden under *Althen* prong two.

b. *Althen* Prong Three

Petitioner has not met her burden pursuant to *Althen* prong two. However, in the interest of completeness, I will complete the third *Althen* prong analysis that requires Petitioner establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281.

Dr. Axelrod argued that Petitioner's menstrual cycle became irregular within one month of her first HPV vaccination on July 22, 2013, and stopped completely within one month of her second HPV vaccination on October 23, 2013. He also noted an influenza vaccination Petitioner received on October 23, 2013, that produced "either a secondary or primary adaptive response," within a month. Pet'r's Ex. 126 at 21. This timeframe is consistent with the Lawley et al. article referenced in Dr. Axelrod's report that revealed the "manifestation of a primary adaptive immune response, which resulted in the production of complement fixing immune complexes, occurred from 10 to 25 days following the initial exposure to the antigen." Pet'r's Ex. 126 at 19 (citing Pet'r's Ex. 147). Furthermore, one month has previously been accepted in the Program as an appropriate timeframe for the manifestation of autoimmune diseases from vaccine-initiated molecular mimicry. *See, e.g.*, *Stewart v. Sec'y of Health & Hum. Servs.,* No. 06-777V, 2011 WL 3241585, at *16 (Fed. Cl. Spec. Mstr. July 8, 2011) (finding the petitioner satisfied *Althen* prong three because the onset of the injury, Guillain-Barré syndrome ("GBS"), occurred within four weeks of a flu vaccine via molecular mimicry). This timeframe, however, is usually applied to acute diseases with a shorter progression than POI, such as GBS. *See, e.g.*, *id.* POI onset determination is further complicated by the measurement of hormone levels on two occasions over several months. Because Petitioner did not present preponderant evidence that she suffers from POI, I cannot apply the onset of her condition (whether based on hormone levels or amenorrhea) to any proposed temporal relationship. Petitioner has therefore failed to meet her burden pursuant to *Althen* prong three.

D. POTS

In the present case, Petitioner has also alleged that her HPV vaccines caused her to develop POTS. In order to be successful on that claim, Petitioner must establish vaccine-causation pursuant to all three *Althen* prongs for that injury.

a. *Althen* Prong One

Petitioner did not present a separate causation theory for POTS. Instead, Dr. Axelrod identified potential, limited, sequence homology between components of the HPV vaccine and fibroblast growth factor receptor 3. Pet'r's Ex. 126 at 16. This brief mention is vague, however, given the relevance of fibroblast growth factor to numerous processes and systems in the body. Dr. Axelrod did not explain how this protein, a signaling molecule that regulates cell activity, is relevant to the autonomic system or POTS, specifically. Dr. Axelrod did not explain why a pathogenic cross-reaction would be more likely to occur following an HPV vaccine and target

fibroblast growth factor receptors in such a way that would lead to the development of POTS. Alternatively, Dr. Axelrod presented evidence of an association between POTS and the hereditary condition, EDS. Dr. Axelrod stated in this report that EDS patients were more likely to also suffer from POTS, but he then acknowledged that "this does not prove that either [EDS] or [POTS] are autoimmune disorder [sic]." *Id.* at 12. Respondent's expert agreed with this association and noted there was no evidence of an autoimmune etiology for POTS or EDS. *See* Resp't's Ex. P at 8.

Dr. Axelrod stated that Petitioner "developed antibodies to autoantigens related to autoimmune [POI] and [POTS], indicating that her immune system lymphocytes are capable of reacting to her ovaries and autonomic myelinated and unmyelinated neurons." Pet'r's Ex. 126 at 17. He described the mechanism with respect to POI. *Id.* He detailed the production of AMH antibodies and hypothesized that the "immune response to her autoantigens related to her ovaries, as well as her autonomic neurons[,] then caused damage to her autonomic nervous system, with the development of [POTS] and autoimmune [POI], which progressed over time." *Id.* While he devoted much time and analysis to relitigating the POI mechanism, he did not develop an independent theory for POTS. Indeed, POTS is essentially relegated to an afterthought, tacked on to arguments clearly developed for POI. As such, there is no meaningful and distinct identification or explanation of a biological mechanism to apply to Petitioner's clinical presentation of autonomic dysfunction.

Petitioner has asserted a molecular mimicry theory with respect to her POI claim. As the two injuries were inextricably linked together in Dr. Axelrod's report, it stands to reason that a molecular mimicry process would also be the basis of her POTS causation theory. Although Petitioner has not claimed as much, I will address this potential argument based on the record as a whole. Petitioner has failed to present evidence that her proposed theory of molecular mimicry would apply to POTS. *See W.C. v. Sec'y of Health & Hum. Servs.,* 704 F.3d 1352, 1360 (2013) (finding that a petitioner cannot prevail by simply invoking the term 'molecular mimicry,' or by showing that molecular mimicry is a valid theory to explain how *other* triggers may have induced *other* diseases and determining that a petitioner must produce additional evidence that molecular mimicry can cause the flu vaccine to cause POTS). If I accepted Petitioner's implication that molecular mimicry could be used to demonstrate an association between any combination of antigens and autoimmune injuries, *Althen* prong one "would be rendered meaningless." *See Caves v. Sec'y of Health & Hum. Servs.,* 100 Fed. Cl. 119, 135 (2011), *aff'd*, 463 F. App'x. 932 (2012); *see also McKown v. Sec'y of Health & Hum. Servs.,* No. 15-1451, 2019 WL 4072113, *50 (Fed. Cl. Spec. Mstr. July 15, 2019) ("[M]erely chanting the words 'molecular mimicry' in a Vaccine Act case does not render a causation theory scientifically reliable, absent additional evidence specifically tying the mechanism to the injury and/or the vaccine in question.").

Lastly, I cannot ignore the fact that to date, no claim has succeeded in the Program that alleged vaccine-caused POTS. Indeed, that pertains to all covered vaccines in the Program. *See, e.g.*, *Hibbard v. Sec'y of Health & Hum. Servs.,* 698 F.3d 1355 (Fed. Cir. 2012) (affirming the special master's dismissal of a case alleging that the flu vaccine caused POTS); *America v. Sec'y of Health & Hum. Servs.,* No. 17-542V, 2022 WL 278151, at *27 (Fed. Cl. Spec. Mstr. Jan. 4, 2022) (ruling against the petitioner's argument that the HPV vaccine can interfere with the nervous system sufficient to cause POTS, autonomic dysfunction or generalized dysautonomia, or vasovagal syncope); *L.P. v. Sec'y of Health & Hum. Servs.,* No. 16-1278V, 2021 WL 2373863, at

*29 (Fed. Cl. Spec. Mstr. Apr. 26, 2021) (rejecting the petitioner's claim that the flu vaccine can cause POTS via the induction of antiphospholipid antibodies); *Hughes v. Sec'y of Health & Hum. Servs.,* No. 16-930V, 2021 WL 839092, at *30 (Fed. Cl. Spec. Mstr. Jan. 4, 2021) (denying compensation for a claim involving the HPV vaccine and POTS); *E.S. v. Sec'y of Health & Hum. Servs.,* No. 17-480V, 2020 WL 9076620, at *49–51 (Fed. Cl. Spec. Mstr. Nov. 13, 2020); *Balasco v. Sec'y of Health & Hum. Servs.,* No. 17-215V, 2020 WL 1240917, at *33–34 (Fed. Cl. Spec. Mstr. Feb. 14, 2020); *Yalacki v. Sec'y of Health & Hum. Servs.,* No. 14-278V, 2019 WL 1061429, at *34 (Fed. Cl. Spec. Mstr. Jan. 31, 2019), *mot. for review den'd*, 146 Fed. Cl. 80 (2019) (finding that the evidence presented to show POTS is autoimmune was thin and that the petitioner failed to show a HPV vaccine likely causes "the production of antibodies associated with autonomic damage or interference sufficient to cause POTS"); *Johnson v. Sec'y of Health & Hum. Servs.,* No. 14-254V, 2018 WL 2051760, at *1 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) (ruling against the petitioner in a case alleging that the HPV vaccine caused POTS and noting that the medical literature suggesting that POTS "might be autoimmune appears [to be] extremely limited"); *L.A.M. v. Sec'y of Health & Hum. Servs.,* No. 11-852V, 2017 WL 527576, at *63 (Fed. Cl. Spec. Mstr. Jan. 31, 2017) (finding that most cases of POTS do not have an autoimmune etiology and that the petitioner's claim that the HPV vaccine caused POTS must fail because she did not provide corroborating evidence of an autoimmune process); *Combs v. Sec'y of Health & Hum. Servs.,* No. 14-878V, 2018 WL 1581672 (Fed. Cl. Spec. Mstr. Jan. 31, 2017); *Turkopolis v. Sec'y of Health & Hum. Servs.,* No. 10-351V, 2014 WL 2872215 (Fed. Cl. Spec. Mstr. May 30, 2014). This is not to say that a future case alleging vaccine-caused POTS cannot and will not succeed in the Program based on the evolving understanding of the post-vaccination pathogenesis of the condition. However, Petitioner's claim is not one of those cases. Therefore, Petitioner has failed to satisfy the first prong of *Althen* by a preponderance of the evidence for her alleged POTS injury.

b. *Althen* Prong Two

Petitioner presented evidence that multiple treaters assessed her with POTS. Dr. T. Chelimsky diagnosed Petitioner with POTS on August 5, 2014. Pet'r's Ex. 4a at 86. Dr. Reber assessed Petitioner with POTS on August 26, 2014. Pet'r's Ex. 3b at 145. And yet, despite a formal diagnosis from Dr. T. Chelimsky, Respondent's expert Dr. Arnold contended that Petitioner does not have POTS. Resp't's Ex. P at 7. Dr. Arnold asserted that despite what Petitioner's treaters believed, Petitioner did not meet the diagnostic criteria for POTS. Dr. Arnold noted Dr. G. Chelimsky's determination in May of 2014, that there was "no evidence of POTS[,]" was based on Petitioner's tilt table test results, despite the presence of autonomic symptoms, including instances "where her heart rate will drop very low for several hours[,]" randomly dilated pupils, and brain fog. *See* Pet'r's Ex. 4a at 26. Indeed, Dr. T. Chelimsky did not rely on filed tilt table test results to support his disagreement with Dr. G. Chelimsky and to formally diagnose Petitioner with POTS in August of 2014. Dr. T. Chelimsky instead relied on Petitioner's symptoms of near syncope, migraines, and other "salient feature[s]" including the "excessive lability of many vegetative processes, including heart rate, estrogen levels (by history)[,] and weight[.]" *See id.* at 86.

Drs. G. and T. Chelimsky both examined and assessed Petitioner over a relatively short period but reached opposite conclusions. There is no indication that Petitioner's clinical presentation changed, or that she had additional test results to explain the different diagnoses. I

find the difference in diagnoses puzzling and will address this unique circumstance in more detail.[72] Dr. G. Chelimsky is the chief of pediatric gastroenterology for the Children's Hospital of Richmond at Virginia Commonwealth University ("VCU").[73] She is board certified in autonomic disorders and a prior director of the pediatric autonomic disorders program, Rainbow Babies at the Children's Hospital at the University of Cleveland.[74] Dr. G. Chelimsky is a leading authority on autonomic disorders and has co-authored several papers on POTS, including *Adolescent fatigue, POTS, and recovery, a guide for clinicians,* and with Dr. T. Chelimsky, *Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome.*[75] Dr. T. Chelimsky is a professor of neurology and the director of the autonomic laboratory at VCU.[76] He is a past president of the American Autonomic Society and is also seen as a leading expert on autonomic disorders, such as POTS.[77] At the time of Petitioner's treatment, Drs. G. and T. Chelimsky were employed by the same medical facility, Wisconsin Children's Hospital Autonomic Reflex Laboratory, in the same area of medicine. *See, e.g.*, Pet'r's Ex. 4a at 26. Certainly, it is reasonable that Dr. T. Chelimsky would have had access to Dr. G. Chelimsky's earlier notes and opinions with respect to Petitioner prior to diagnosing her. It is unknown why Dr. T. Chelimsky would disregard those notes and overrule the expertise of Dr. G. Chelimsky without direct explanation. Dr. G. Chelimsky's opinion in May of 2014 was unequivocal, as was Dr. T. Chelimsky's diagnosis in August of the same year. Neither should be disregarded, nor do they cancel each other out. The level of expertise of both treaters warrants careful consideration of their respective diagnoses and rationale. I will consider both assessments in the context of Petitioner's entire medical record. Additionally, two years later in 2016, Petitioner's cardiologist noted that Petitioner did not have symptoms consistent with POTS.

Petitioner did not submit medical literature or an expert discussion of a POTS clinical presentation similar to hers. I am not a physician, and it is not my role to diagnose Petitioner. She had at least two treaters who found her symptoms indicative of POTS and at least two that did not. I find that there is some reasonable disagreement among the medical professionals in this case concerning Petitioner's POTS diagnosis. The Program places a premium on the opinions of real-time treaters, and I will do the same. I find that Petitioner has presented preponderant evidence that she suffered from some variation of POTS.

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[72] To that end, to provide background information on the treaters and context for my in-depth analysis of and reliance on their respective diagnoses, I reference publicly available biographical information in this Decision. The source material for such information is included in this Decision as attachments. *See* Appendices A–C.

[73] *Introducing our new chief of pediatric gastroenterology: Q & A with Dr. Gisela Chelimsky,* CHILDREN'S HOSPITAL OF RICHMOND AT VCU (Mar. 7, 2022), https://www.chrichmond.org/blog/introducing-our-new-chief-of-pediatric-gastroenterology-qa-with-dr-gisela-chelimsky.

[74] *Gisela G. Chelimsky, MD,* MEDICAL HOME PORTAL, https://www.medicalhomeportal.org/author/286 (last visited Mar. 31, 2023).

[75] *See id.*

[76] *VCU Department of Neurology Welcomes Dr. Thomas Chelimsky,* VCU (Mar. 22, 2022), https://neurology.vcu.edu/news/department-of-neurology-welcomes-dr-thomas-chelimsky/#:~:text=Thomas%20C.,of%20neurology%20and%20department%20chair.

[77] *See id.*

Her burden does not end there, however. Petitioner must still apply her biological mechanism for vaccine causation to her alleged injury. Petitioner did not present preponderant evidence of a biological mechanism pursuant to prong one. She did not present preponderant evidence that POTS can be autoimmune in nature or that her POTS was autoimmune. Without a logical sequence of cause and effect applying a biological mechanism to Petitioner's condition, Petitioner has not presented preponderant evidence to meet her burden pursuant to *Althen* prong two with respect to her POTS injury.

c. *Althen* Prong Three

As Petitioner did not present preponderant evidence of a biological mechanism for vaccine-caused POTS, there is no identified timeline to assess what would be an appropriate symptom progression. Dr. Axelrod did not identify an appropriate temporal relationship for vaccine-caused POTS, aside from the timeframe he argued was applicable to Petitioner's POI claim. Therefore, I am left only able to apply the same timeframe for both injuries.

Petitioner was first diagnosed with POTS by Dr. T. Chelimsky in August of 2014. It is notable that when Dr. G. Chelimsky first assessed Petitioner in May of the same year, Dr. G. Chelimsky wrote Petitioner's objective testing did not show evidence of POTS. Pet'r's Ex. 4a at 31. In diagnosing Petitioner with POTS in August of 2014, Dr. T. Chelimsky did not describe any change in Petitioner's clinical presentation since Dr. G. Chelimsky's prior determination in May of 2014 that Petitioner showed no evidence of POTS. *See id.* at 31, 86. Instead, Dr. T. Chelimsky noted Petitioner's changes in heart rate, estrogen levels, and weight. However, these fluctuations were also present prior to May of 2014, and to some extent, were explicitly noted by Dr. G. Chelimsky in May of 2014. *See* Pet'r's Ex. 4a at 26 (a May 12, 2014 medical record noted that Petitioner's heart rate would drop very low for several hours). Dr. T. Chelimsky also did not detail the addition of any autonomic symptoms or rely on any objective testing from May of 2014 to August of 2014 that could establish the onset of Petitioner's POTS or explain his diagnosis. Dr. G. Chelimsky's notes from Petitioner's exams through May of 2014 make it clear, however, that Petitioner's treaters did not see persuasive evidence of POTS at least up to that point.

Given that, I find that it is more likely than not that in diagnosing Petitioner with POTS in August of 2014, Dr. T. Chelimsky relied on some factor that Dr. G. Chelimsky did not previously see or consider in Petitioner during her May 2014 exam. This material change in symptoms likely emerged sometime after Petitioner's May 12, 2014 exam with Dr. G. Chelimsky and sometime before her formal diagnosis on August 5, 2014, by Dr. T. Chelimsky. At the approximate point of this change, there is preponderant evidence that Petitioner was manifesting evidence of POTS. Even assuming that this change in Petitioner's presentation of POTS symptoms started immediately in mid to late May following her May 12, 2014 visit with Dr. G. Chelimsky, a seven-month lapse between Petitioner's October 2013 vaccination and symptom onset is too remote in time to be attributable to either of the HPV vaccines at issue. The interim negative tilt table testing in May of 2014 provides the most persuasive support that Petitioner's ultimate diagnosis in August of 2014 is not a timely result of molecular mimicry. Therefore, Petitioner has failed to present preponderant evidence to meet her burden pursuant to *Althen* prong three for her POTS claim.

VIII. Conclusion

Petitioner has failed to establish by preponderant evidence that the HPV vaccines she received on July 22, 2013, and October 23, 2013, caused her to develop POI or POTS, as she cannot establish it more likely that she suffers from POI or that her POTS has an autoimmune etiology. While I am sympathetic towards Petitioner's condition and acknowledge that she has suffered both physically and emotionally, the evidence in the record does not show entitlement to compensation by a preponderant standard. Accordingly, this case is hereby **DISMISSED**.[78]

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[78] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.

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Introducing our new chief of pediatric gastroenterology: Q&A with Dr. Gisela Chelimsky

MARCH 07, 2022

Getting to know Dr. Gisela Chelimsky, leading expert in autonomic conditions

Dr. Gisela Chelimsky is a leading expert in neurogastroenterology and autonomic disorders and recently joined our team as chief of pediatric **gastroenterology**(/services/gastroenterology-and-nutrition). She will spend her first few months at CHoR focusing on further growth of our GI program. She's not yet seeing patients, but is busy behind the scenes growing her autonomic team, hepatology services and all areas of GI – including clinical care, research and education. Dr. Chelimsky explains her approach to working with kids and families, and her vision for the future of GI care at CHoR.

What drew you to specialize in pediatric gastroenterology?

My top career choices were pediatric neurology and gastroenterology. I liked the idea of procedures in addition to clinical work, so I decided on gastro. I've come full circle though. In my work with autonomic conditions, I'm able to incorporate my love of both specialties.

Patients travel across the country for your expertise in autonomic conditions. What's unique about the care you provide?

In large part it's that I work with my husband who is an autonomic neurologist. They don't come to see us because we're any smarter than anyone else, but our collaborating allows us to work in a more comprehensive way in trying to understand the mechanisms of disease.

Autonomic disorders are the result of the body not being able to regulate involuntary body functions. As a GI specialist, I work with patients experiencing neuro/gastro and autonomic conditions such as cyclic vomiting disorder, chronic idiopathic nausea and motility disorders, all of which are often associated with other symptoms. These overlapping symptoms are now called Chronic Overlapping Pain Conditions (COPC). Many patients are coming to us with chronic fatigue and pain that doesn't show up in scans and tests. We work together, along with colleagues in **physical therapy**(/services/therapy-services/physical-therapy), **occupational therapy**(/services/therapy-services/occupational-therapy), **psychology**(/services/mental-health) and other specialties, using a biobehavioral approach to treatment which includes physical therapy, cognitive behavioral therapy, exercise and other lifestyle changes. When we use medications, we only use non-addictive options to help modulate the pain or improve the motility. We also see younger kids with undiagnosed GI/neurological conditions, working very closely with **genetics**(/services/genetics) in these cases. We're always looking to determine what role the brain is playing or how the way the brain connects with the rest of the body is making the person respond the way they are.

We're the combination of two people who believe in our patients. We don't dismiss them, and we think outside the box. I think that's what makes us different.

What is your goal when you're working with children and families?

A lot of the teens I see with COPC – or combinations of conditions such as irritable bowel syndrome, fibromyalgia, migraines, chronic fatigue and others – have been told in the past that their symptoms are related to anxiety or depression, and there's nothing that can be done. The first thing I tell them is, "I believe you. I believe in your symptoms." I often joke that this is what I do for a living. If I didn't believe my patients, I'd be bankrupt!

I also explain that what they're experiencing is the result of a software problem, not a hardware problem. Their brain is wired differently, which is why they may have had several GI scopes that didn't find anything but that doesn't mean there's nothing wrong. Then I spend time teaching them how we are going to care for them. Yes, we may use medications, but not in a primary way. Our primary approach is biobehavioral. We'll take baby steps. If they've been curled up in bed, maybe the first step is sitting up with their legs hanging off the edge of the bed as we start challenging their body to a more upright position.

We don't have a magic pill, and we cannot address their issues in a 15-minute appointment. I spend an hour with my patients at each visit to address all their symptoms and develop a thorough approach to care that's built on trust.

Can you explain the brain/gut axis and why it's so important to consider when providing care?

The brain coordinates how the gut moves and receives signals from the body, which the brain then interprets as pain, bloating, nausea, etc. The brain makes the decision of what is painful and what isn't. When a person needs to have a bowel movement, the colon begins contracting. Most of us don't even notice, but kids with autonomic and chronic pain issues often register this as increased sensations of pain. The bodies of people with chronic pain are in excessive sympathetic mode with lower parasympathetic (also called vagal) responses which contribute to the physical reactions and overlap of symptoms.

The opposite of this would be the example of the football player who broke their leg but is so focused on winning the game they don't realize until later that it hurts.

The brain/gut axis is pivotal to our approach to care as we work to change the way the body is perceiving signals and registering symptoms.

What's your vision for our Division of Gastroenterology and Nutrition?

I have a huge vision! We have the right **team(/find-a-provider?specialty=gastroenterology%20and%20nutrition)** and facilities to be a top program in the country. In terms of patient care, I want to expand our clinics

for inflammatory bowel disease, feeding, eosinophilic esophagitis and neurogastrointestinal disorders. I'd like to partner with the adult GI team to provide seamless care for patients from birth to 100.

With the exciting news about **VCU Health's new Institute for Liver Disease and Metabolic Health (https://www.vcuhealth.org/news/institute-for-liver-disease-and-metabolic-health-what-vcus-newest-institute-means),** there is great opportunity for developing our liver transplantation services in pediatrics as well. We'll be looking to bring two hepatologists onto the team in this process.

I also want to increase our role with medical students and residents and develop a pediatric gastroenterology fellowship program. This next generation of providers is who's going to continue our work.

Lastly, we'll be investing in **research(/research)**. We can't be a top GI program with clinical work alone. Faculty come to an academic medical institution to grow in this area and we want to allow them the time and space to do so. Research also brings new technology and innovation, which feeds better patient care.

These are the pillars of an academic medical center – patient care, education and research – and we'll be cultivating all three.

What do you want patients, families and referring providers to know about you?

Our team is here for them. We're working hard to increase availability and make it easier to make appointments for common concerns, as well as complex issues that have been difficult to diagnose and treat elsewhere. We want to be in the community, so they have easy access to us while we're continually improving patient care and incorporating research.

I want patients to know that I believe in family-centered care where the child and caregivers are key members of the team. They're important and they deserve to be heard without feeling hurried.

For pediatricians, we will get back to them when they call, and they will get a letter after every visit. Whether they're looking to refer a patient or for advice on next steps, we're here for them and for the kids.

Continued growth of our people and programs is fueled by Children's Hospital Foundation(/childrens-hospital-foundation) and generous donors in our community. Your support helps us recruit and retain top talent like Dr. Chelimsky.

Discover our full range of gastroenterology and nutrition care for kids at CHoR.(/services/gastroenterology-and-nutrition)

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Gisela G. Chelimsky, MD

Professor
Department of Pediatrics, Division of Pediatric Gastroenterology
Medical College of Wisconsin
and
Children's Wisconsin

Gastroenterology - Children's
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Biosketch:
Gisela Chelimsky, MD, is Professor of Pediatrics at the Medical College of Wisconsin. Dr. Chelimsky was previously Professor of Pediatrics and Neurology at Case Western Reserve University School of Medicine in Cleveland where she served as Director of Pediatric Autonomic Disorders Program Rainbow Babies and Children's Hospital at University Hospitals of Cleveland. A graduate of Medical School at the University of Buenos Aires, Argentina, Dr. Chelimsky completed residency in Pediatrics and pediatric gastroenterology fellowship at Rainbow Babies and Children's Hospital in Cleveland Ohio. Dr. Chelimsky joined the faculty at Case Western in 1996 and rose to the rank of Professor in 2011. She is also board certified in Autonomic Disorders.

Dr. Chelimsky has published more than 50 original articles, contributed to 17 books or chapters, and made multiple presentations at regional, national and international meeting. Her work has focused on functional gastrointestinal disorders, the autonomic nervous system and understanding the inter-relations between the brain-gut axis and the co-morbidities that come with these disorders. Furthermore, she has been for the past 10 years a co-investigator in an NIH-NIDDK funded grant in pelvic pain understanding the role of comorbidities and the autonomic nervous system in these disorders.

No conflicts of interest (07/14/2022).

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VCU Department of Neurology Welcomes Dr. Thomas Chelimsky

By Shea Wright
Neurology

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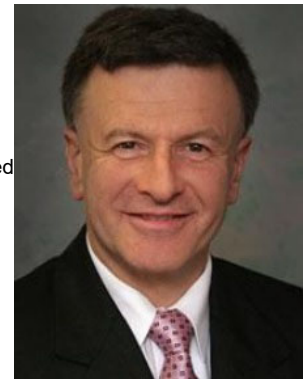
March 22, 2022



The VCU Department of Neurology welcomes Dr. Thomas C. Chelimsky, a professor of Neurology and the Director of VCU's Autonomic Laboratory.

Dr. Chelimsky joined VCU on February 1, 2022, from the Medical College of Wisconsin where he held positions of tenured professor of neurology and department chair. In a previous appointment at Case Western Reserve University in 1993 he opened the second autonomic lab in the country. He also directed the Case Pain Center from 1994 to 2004, which led to founding and becoming CEO of PainSTakers, an educational company currently dedicated to training doctors, physical therapists, and behaviorists in the non-pharmacological approach to chronic pain management.

Dr. Chelimsky, is an early pioneer in the field of functional autonomic disorders such as POTS (postural tachycardia syndrome), and pediatric functional gastrointestinal disorders and has published over 85 peer-reviewed articles. He has received continuous funding by NIH since 2009 to study the interface between pelvic pain and autonomic dysfunction and is past-president of the American Autonomic Society (AAS) where he held multiple positions, and past chair of both the American Academy of Neurology's (AAN) Pain and Autonomic Sections. He has been instrumental in fellow board certification and fellowship accreditation in Autonomic Disorders through the United Council for Neurologic Subspecialties (UCNS) where he chaired the first examination committee.

In his new role, Dr. Chelimsky's interests and enthusiasm will focus on a rich collaboration with VCU faculty members over many disciplines to develop an autonomic program that crosses traditional boundaries to include both children and adults, to offer both interdisciplinary diagnostic services and an on-site interdisciplinary treatment program, and to foster robust clinical, research and educational components.

As a child Dr. Chelimsky had a small role in the movie *Charade* with Audrey Hepburn and Cary Grant, but ultimately chose medicine as his field of choice.

Dr. Chelimsky graduated from Washington University Medical School in St. Louis, MO, and completed his residencies at Mayo Clinic in both internal medicine and neurology, where he was their first fellow in autonomic disorders.