In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 30, 2021

LAKIA BRAYBOY,	*	No. 15-183V
Petitioner,	*	Special Master Sanders
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Ruling on *Althen* Prong One; Human Papillomavirus ("HPV") Vaccine; Primary Ovarian Insufficiency/Failure ("POI")
Respondent.	*	

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

RULING ON *ALTHEN* PRONG ONE[1]

This matter concerns eight petitioners[2] who have filed petitions for compensation in the National Vaccine Injury Compensation Program ("the Program").[3] The petitioners have alleged that human papillomavirus ("HPV") vaccinations they received between 2008 and 2013 caused them to suffer primary ovarian insufficiency/failure ("POI").[4] The petitioners have consolidated

[1] This Ruling 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). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete 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 Ruling. If, upon review, I agree that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] This ruling will be filed in *Alexander* (14-868V); *Bello* (13-349V); *Bond* (16-1615V); *Drummond* (16-702V); *Nunez* (14-996V); *Root* (16-20V); *Tilley* (14-818V); and *Brayboy* (15-183V), which is the named case.

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

[4] Primary ovarian insufficiency, also known as premature or primary ovarian failure, is the "absence or irregularity of menses lasting at least four months, with menopausal levels of serum gonadotrophins in an adolescent girl or woman under 40 years of age. It may be temporary or permanent." Primary Ovarian Insufficiency, DORLAND'S MEDICAL DICTIONARY ONLINE [hereinafter "DORLAND'S"], https://www.dorlandsonline.com (last visited June 23, 2021). Gonadotropins are "any hormone[s] that stimulate[ ] the gonads[.]" Gonadotropin, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). Gonads, also referred to as genital glands and sex glands, are "gamete-producing gland[s,]" such as ovaries. Gonad, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

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their claims for the purpose of determining whether they have presented a sufficient causation theory pursuant to *Althen* prong one. For the reasons discussed herein, I find that the petitioners have satisfied *Althen* prong one. Petitioners have articulated a sound and reliable theory of how HPV vaccines could cause autoimmune POI via molecular mimicry. More specifically, Petitioners' expert 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.

I. Procedural History

Several petitioners in recent years have filed claims alleging that they suffered POI due to HPV vaccinations. Those cases were contested by Respondent, who argued that many of the claims were barred from entitlement because the statute of limitations had run. The special master presiding over the cases determined that case timeliness would depend on the onset of each petitioner's POI. On November 20, 2014, the special master held a status conference and identified the cases in which a finding regarding onset was relevant to the statute of limitations or causation, even if timeliness was not an issue. *See, e.g.*, *Bello*, No. 13-349V, ECF No. 53 at 1. During the status conference, "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." *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). The special master established that the *Culligan* case would serve as the test case, with all others trailing, and 1) "a timeliness determination would be made based on the evidence presented at the *Culligan* hearing;" 2) all petitioners would consent to share their medical records; and 3) "similar hearings would not be conducted in other POI cases[.]" *Id.* at *3–*4.

In advance of the onset hearing, the special master ordered petitioners to file an expert report addressing several questions, including "what constitutes 'the first symptom or manifestation of [POI/POF] onset[.]'" *Id.* (citing *Cloer v. Sec'y of Health & Hum. Servs.*, 654 F.3d 1322, 1340 (Fed. Cir. 2011)). A consolidated hearing regarding the issue of onset of POI was held in June 2015, after which the cases discussed below have been allowed to proceed to a determination on entitlement. *See* Sched. Order, ECF No. 15; *see also Culligan*, 2016 WL 3101981, at *5. *Culligan* was ultimately dismissed after the special master determined the case was time-barred. *See Culligan*, 2016 WL 3101981, at *11.

Following the special master's decision in *Culligan*, petitioners' counsel indicated that he would likely retain the same causation expert for all of the cases, and Respondent indicated that his stance on consolidation may depend on whether the petitioners all presented the same theory of causation. *E.g.*, No. 15-183V, ECF No. 15 at 1. After initial expert reports were filed in all cases, the parties ultimately agreed that consolidation remained appropriate to determine if any of the cases could proceed in light of the causation theory that had been proposed in each of the petitioners' cases. *See, e.g.*, No. 15-183V, ECF No. 41. I will now address whether these consolidated cases can meet their burden with respect to *Althen* prong one.

A. Trailing Cases

a. Bello

On May 22, 2013, Cristal Bello filed the first of these cases, alleging in her petition that an HPV vaccine she received on June 4, 2010, caused her to develop POI. No. 13-349V, Pet. at 1, ECF No. 1. She filed medical records on July 12, 2013, October 3, 2013, and December 13, 2013. ECF Nos. 8, 15, 23. On February 20, 2014, Respondent filed his Rule 4(c) report and denied that Petitioner was entitled to compensation. ECF No. 35 at 7. Petitioner filed additional medical records on July 16, 2014, and November 18, 2014. ECF Nos. 46, 52. Pursuant to the presiding special master's consolidation of this case following *Culligan*, Petitioner filed a status report on September 8, 2016, indicating "consent[] to the disclosure of her case information to other POI petitioners, including the POI petitioners whose petitions were filed after [after *Culligan*]." ECF No. 73 at 2; ECF No. 76. Petitioner submitted additional medical records on January 5, 2017, and March 23, 2017, as well as a final statement of completion on March 23, 2017. ECF Nos. 80, 90–92.

b. Tilley

On September 5, 2014, Lisa Tilley filed a petition in which she claimed that her then-seventeen-year-old daughter, Olivia Tilley, suffered from POI as a result of HPV vaccines administered on June 26, 2009, August 26, 2009, and August 10, 2011. No. 14-818V, Pet. at 1, ECF No. 1. The case caption was amended on June 15, 2015, because Olivia Tilley reached the age of majority. ECF No. 19 at 1. Petitioner filed medical records on September 30, 2014. ECF No. 8. On October 1, 2014, Petitioner submitted a status report indicating that her case should be included in the POI/POF onset cases and that she consented to disclosure of her case information. ECF No. 9 at 1. During the November 20, 2014 status conference, the presiding special master stated that this case would trail *Culligan* because an onset determination was necessary for this case to proceed. ECF No. 15 at 1. Following the *Culligan* decision and August 11, 2016 status conference, Petitioner filed a status report indicating consent to disclosure of her case information to other POI petitioners. ECF No. 25. On September 28, 2016, Respondent contested Petitioner's entitlement to compensation in a Rule 4(c) report. ECF No. 27 at 5. Petitioner filed additional medical records on November 1, 2016, and January 5, 2017, as well as a final statement of completion on January 5, 2017. ECF Nos. 28, 32–33.

c. Alexander

On September 18, 2014, Howard and Sharyn Alexander filed a petition alleging that their then-eighteen-year-old daughter, Whitney Alexander, experienced POI due to HPV vaccines she received on February 25, 2008, April 28, 2008, and October 15, 2008. No. 14-868V, Pet. at 1, ECF No. 1. The caption was amended to identify Whitney Alexander as the sole petitioner on June 15, 2015. ECF No. 20. Petitioner filed medical records and her affidavit on October 1, 2014. ECF Nos. 8–9. On October 1, 2014, Petitioner indicated that her case should be included in the POI cases which required a finding of onset prior to a determination of causation, which the presiding special master acknowledged during the November 20, 2014 status conference. ECF No. 10 at 1; ECF No. 15 at 1. Petitioner indicated in her status report that she consented to disclosure of her case information to the other POI petitioners. ECF No. 10 at 1. Following *Culligan* and the August 11, 2016 status conference, Petitioner reaffirmed her consent to disclosure on September 8, 2016. ECF No. 32. Respondent filed his Rule 4(c) report asserting that compensation was inappropriate in this case on September 29, 2016. ECF No. 34 at 2. Petitioner filed additional medical records and a final statement of completion on November 3, 2016. ECF Nos. 35–36.

d. Nunez

On October 16, 2014, Monica Chenowith filed a petition and alleged that her then-seventeen-year-old daughter, Alexandra Nunez, suffered POI as a result of HPV vaccines administered on October 20, 2011, and January 4, 2012. No. 14-996V, Pet. at 1, ECF No. 1. On June 15, 2015, the presiding special master amended the case caption to reflect that Alexandra Nunez had reached the age of majority. ECF No. 14. During the November 20, 2014 status conference, the presiding special master identified this case as one in which an onset finding was relevant to causation even though the statute of limitations was not then at issue. ECF No. 7 at 1. Petitioner filed medical records on November 25, 2014. ECF No. 8. On December 9, 2014, Petitioner filed a status report indicating consent to the disclosure of her case information to other POI petitioners. ECF No. 10. Petitioner filed additional medical records on December 16, 2014. ECF No. 11. On June 21, 2016, following *Culligan*, the presiding special master held a status conference to discuss whether this case was precluded from proceeding on statute of limitations grounds. ECF No. 19 at 1. The presiding special master did not make a finding regarding preclusion at that time but instead ordered Petitioner to submit additional medical records. *Id.* Petitioner filed her status report reaffirming her consent to the disclosure of her case information on September 8, 2016. ECF No. 23. Petitioner submitted additional medical records on October 12, 2016, and November 1, 2016, and a statement of completion on the latter date. ECF Nos. 26, 28–29. The presiding special master held a status conference on December 12, 2016, to again discuss whether Petitioner's case was time-barred. ECF No. 33 at 1. The presiding special master concluded that, based on the medical records, "this case would not be considered presumptively time-barred[]" and would "move forward with the same deadlines as the remaining consolidated [POI] cases." *Id.*

e. Brayboy

On February 26, 2015, Lynette Brayboy filed a petition as the parent of then-fifteen-year-old LaKia Brayboy. No. 15-183V, Pet. at 1, ECF No. 1. Petitioner alleged that LaKia Brayboy experienced POI due to HPV vaccines administered on July 21, 2012, September 26, 2012, and February 6, 2013. *Id.* The case caption was amended on December 28, 2016, to reflect that LaKia Brayboy had reached the age of majority. ECF No. 29. Petitioner filed medical records on March 2, 2015. ECF No. 5. Also on March 2, 2015, Petitioner filed a status report indicating that she would participate as a trailing case in the *Culligan* onset matter. ECF No. 6. In her status report, Petitioner consented to the disclosure of her information to the other POI petitioners. *Id.* On September 8, 2016, Petitioner filed her status report indicating consent to the disclosure of her case information. ECF No. 16. On September 19, 2016, Respondent filed a Rule 4(c) report denying that Petitioner had demonstrated entitlement to compensation. ECF No. 17 at 5. Petitioner filed additional medical records on September 28, 2016, October 12, 2016, and November 3, 2016, as well as a final statement of completion on November 3, 2016. ECF No. 20–21, 23–24. On December 28, 2016, Petitioner filed a status report indicating that she consented to disclosure of her information to other POI petitioners. ECF No. 31.

f. Root

On January 5, 2016, Frederick and Lisa Root filed a petition alleging that their then-fifteen-year-old daughter, M.A.R., suffered from POI due to HPV vaccines she received on January 21, 2013, March 8, 2013, and August 26, 2013. No. 16-20V, Pet. at 1, ECF No. 1. Petitioners filed medical records on January 26, 2016. ECF Nos. 7–8. On August 25, 2016, Respondent filed a Rule 4(c) report denying that Petitioners were entitled to compensation. ECF No. 15 at 5.

Petitioners submitted a status report indicating consent to disclosure of their case information to other POI petitioners on September 8, 2016. ECF No. 17. On October 31, 2016, Petitioners filed additional medical records and a statement of completion. ECF Nos. 21–22.

g. Drummond

On June 16, 2016, Grace Drummond filed a petition alleging that she "suffered Postural Orthostatic Tachycardia Syndrome ("POTS"),[5] and diminishing ovarian reserve leading to [POI]" as a result of HPV vaccines she received on July 22, 2013 and October 23, 2013. No. 16-702V, Pet. at 1, ECF No. 1. She filed medical records on July 11, 2016. 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 submitted additional medical records between September 2016 and January 2017 and a statement of completion on January 24, 2017. ECF Nos. 15–16, 19, 23–24, 28–29.

h. Bond

On December 6, 2016, Mary Ellouise Bond filed a petition and claimed that she suffered POI due HPV vaccines administered on February 15, 2013, April 23, 2013, and September 27, 2013. No. 16-1615V, Pet. at 1, ECF No. 1. She submitted medical records along with her petition as well as a statement of completion on December 12, 2016. ECF Nos. 1, 6. In his Rule 4(c) report filed on March 2, 2017, Respondent argued that Petitioner had not demonstrated entitlement to compensation. ECF No. 11 at 4. I held a Rule 5 status conference on April 6, 2017, and ordered Petitioner to submit an expert report regarding causation. ECF No. 12. On August 3, 2017, I held an additional status conference with the parties, and we discussed whether Petitioner would join her case with the other POI cases. I ordered Petitioner to file a status report indicating how she wished to proceed. ECF No. 17. Instead, Petitioner's attorney filed a motion to withdraw on August 24, 2017, due to a conflict of interest. ECF No. 18. The attorney then-representing the other POI petitioners began representing Petitioner. *See* ECF Nos. 19–21.

B. *Althen* Compartmentalization

The presiding special master held a status conference regarding how to proceed with the consolidated POI cases on December 1, 2016. No. 15-183V,[6] Sched. Order at 1, ECF No. 26. In addition to agreeing that the POI petitioners would submit outstanding medical records, the parties agreed that they would file expert reports regarding all three *Althen* prongs. *Id.* The parties also indicated that they would explore how to further proceed once expert reports were filed in the record. *Id.*

On August 1, 2017, Petitioner Brayboy filed an expert report from Dr. Yehuda Shoenfeld, regarding her theory of causation. Pet'r's Ex. 17, ECF No. 40-4. This expert report authored by Dr. Shoenfeld has been filed in support of each of the POI petitioners' cases and does not discuss case-specific information. The report was filed in *Bello*, *Alexander*, *Nunez*, *Root*, and *Tilley* on

[5] Postural Orthostatic Tachycardia Syndrome refers to "a group of symptoms (not including hypotension) that sometimes occur when a person assumes an upright position, including tachycardia, tremulousness, lightheadedness, sweating, and hyperventilation[.]" *Postural Orthostatic Tachycardia Syndrome*, DORLAND'S, https://www.dorlandsonline.com (last visited June 23, 2021).

[6] All further docket citations will refer to this case unless otherwise noted.

August 1, 2017, in *Drummond* on August 2, 2017, and in *Bond* on January 10, 2018.[7] Petitioner Brayboy also produced reports on August 1, 2017, from Drs. Orit Pinhas-Hamiel and Felice Gersh, which were tailored to her specific case, as well as a piece of medical literature. Pet'r's Exs. 11, 15, ECF Nos. 39–40. Drs. Pinhas-Hamiel and Gersh also filed case-specific reports in the other POI cases.[8] Petitioner Brayboy followed up with additional medical literature on September 26, 2017 and January 3, 2018. ECF Nos. 42–48, 50.

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 petitioners presented the same causation theory in each of the consolidated POI cases. ECF No. 41. I ordered Respondent to produce an expert report in accordance with his suggestion. *Id.* Respondent filed expert reports from Drs. Thomas Forsthuber, David Frankfurter, and Robert Yokel, as well as accompanying medical literature, on May 14, 2018. Resp't's Exs. A, C, E, ECF Nos. 53–58. Respondent filed additional medical literature on compact discs on June 18, 2018. ECF Nos. 59–60.

On September 11, 2018, Petitioner filed responsive supplemental expert reports from Drs. Pinhas-Hamiel and Shoenfeld in support of the POI petitioners' claims. Pet'r's Exs. 77, 78, ECF No. 62. Petitioner filed an additional piece of medical literature on October 17, 2018. ECF No. 63. Respondent filed responsive supplemental expert reports from Drs. Forsthuber, Frankfurter, and Yokel on November 19, 2018. Resp't's Exs. G, H, I, ECF No. 65. Respondent filed additional medical literature on a compact disc on December 10, 2018. ECF No. 67.

Petitioner filed an additional expert report from Dr. Shoenfeld on May 6, 2019, and medical literature the next day. Pet'r's Ex. 80, ECF Nos. 73–74. Respondent then filed additional expert reports from Drs. Forsthuber and Frankfurter on September 30, 2019, as well as medical literature on September 27, 2019 and September 30, 2019. Resp't's Exs. K, L, ECF Nos. 76–78. Petitioner submitted additional medical literature on October 1, 2019. ECF No. 79.

I held a status conference with the parties on December 6, 2019. Sched. Order at 1, ECF No. 80. I explained to the parties that "the next step for the group of petitioners with claims alleging premature ovarian failure following HPV is to present arguments with respect to the viability of a causation theory pursuant to *Althen* prong one." *Id.* I indicated that "the best way to proceed is for the parties to submit briefs supported by the literature and expert opinions as needed." *Id.* Although the facts in each case vary, the causation theory asserted in all the cases was the same and the same experts were used. In order for the experts to provide some degree of specificity to their opinions, the parties agreed that the facts from one case could be used for context. *Id.* The Brayboy case was ultimately selected as the lead case. *See id.* Because the POI petitioners' counsel requested the

[7] *See* No. 13-349V, ECF No. 98-6; No. 14-868V, ECF No. 47-4; No. 14-996V, ECF No. 42-4; No. 16-20V, ECF No. 33-4; No. 14-818V, ECF No. 42-3; No. 16-702V, ECF No. 37-4; No. 16-1615V, ECF No. 23-5.

[8] Reports from Drs. Pinhas-Hamiel and Gersh were filed on August 1, 2017 in *Bello*, *Alexander*, *Nunez*, *Root*, and *Tilley*. *See* No. 13-349V, ECF Nos. 98-2, 98-4; No. 14-868V, ECF Nos. 46-2, 47-2; No. 14-996V, ECF Nos. 41-2, 42-2; No. 16-20V, ECF Nos. 32-2, 33-2; No. 14-818V, ECF Nos. 41-1, 42-2. In *Drummond*, the petitioner filed a report from Dr. Gersh on August 2, 2017, but did not file a case specific report from Dr. Pinhas-Hamiel. *See* No. 16-702V, ECF No. 37-2. In *Bond*, the petitioner filed reports from Drs. Pinhas-Hamiel and Gersh on January 10, 2018. *See* No. 16-1615, ECF Nos. 23-1, 23-3.

opportunity to use facts from the Brayboy case briefings, I ordered counsel to obtain Health Insurance Portability and Accountability Act ("HIPAA") waivers from each of the petitioners. *Id.*

Petitioner filed her Authorization to Disclose Health Information and Other Records pursuant to HIPAA [hereinafter "HIPPA waiver"] on February 4, 2020, to allow her filings to be shared with the other petitioners in the consolidated POI cases. ECF No. 81. Root filed a HIPAA waiver on February 4, 2020.[9] No. 16-20V, ECF No. 78. Nunez and Tilley also filed HIPAA waivers on February 4, 2020. No. 14-996V, ECF No. 83; No. 14-818V, ECF No. 85. On February 5, 2020, Alexander filed her HIPAA waiver. No. 14-868V, ECF No. 91. Bond and Drummond filed HIPAA waivers on February 28, 2020. No. 16-1615V, ECF No. 66; No. 16-702V, ECF No. 84. Bello filed her HIPAA waiver on May 1, 2020. No. 13-349V, ECF No. 145.

On June 18, 2020, Petitioner[10] filed medical literature as well as her brief regarding *Althen* prong one. ECF Nos. 85–86. Respondent followed with medical literature and his response to Petitioner's brief on September 22, 2020. ECF Nos. 87–88. Petitioner filed her reply on November 20, 2020. ECF No. 90.

II. Experts

A. Petitioner's Expert, Dr. Yehuda Shoenfeld, M.D.

Dr. Shoenfeld received his medical degree from the Hebrew University's Hadassa Medical School in Israel in 1972. Pet'r's Ex. 24 at 2, ECF No. 40-3. He was appointed a Professor of Medicine at Tel-Aviv University, Sackler Faculty of Medicine in 1990 and has been the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at that university since 2003. *Id.* at 2, 4. Dr. Shoenfeld has also been the Head of Zabludowicz Center for Autoimmune Diseases at the Sheba Medical Center in Israel since 2011. *Id.* at 2. Additionally, he has been the Head of the Hybridoma Unit and Research Laboratory for Autoimmune Diseases at Soroka Medical Center since 1985 as well as the Head of Department of Medicine at "B" Sheba Medical Center and the Head of the Center for Autoimmune Diseases at Tel-Aviv University since 1989. *Id.* Dr. Shoenfeld has authored or co-authored over 1,900 articles, fifty books, and 158 chapters in medical texts, many of them focusing on autoimmune diseases. *See id.* at 22–139. He has served on the editorial boards of numerous journals. *See id.* at 9–12.

B. Petitioner's Expert, Dr. Orit Pinhas-Hamiel, M.D.

Dr. Pinhas-Hamiel received his medical degree from the Sackler School of Medicine at Tel-Aviv University in Israel in 1986. Pet'r's Ex. 12 at 1, ECF No. 39-2. He has been Head of the National Juvenile Diabetes Center at Maccabi Health Care Services since 2000. *Id.* at 4. Dr. Pinhas-Hamiel has also been Head of the Endocrine and Diabetes Unit at Edmond & Lily Safra Children's Hospital, which is part of The Chaim Sheba Medical Center, in Israel since 2002. *Id.* He is the author or co-author of eighty-nine articles as well as numerous case reports, review

[9] Although M.A.R. had reached the age of majority prior to this date, Lisa Root was her designated health care proxy and both Lisa and Frederick Root had power of attorney. Root Ex. 115 at 3–4, ECF No. 78-1. Lisa Root signed the HIPAA waiver. *Id.* at 2.

[10] As the Brayboy case was selected to be the lead, or named, case for the POI petitioners, the briefs in support of *Althen* prong one were filed in her case only but on behalf of all POI petitioners.

articles, book chapters, and other works. *Id.* at 11–62. He has been a member of the editorial boards of Pediatric Diabetes and Frontiers in Endocrinology since 2011 and a member of the World Journal of Diabetes editorial board since 2014. *Id.* at 63.

C. Petitioner's Expert, Dr. Felice Lauren Gersh, M.D.

Dr. Gersh received her medical degree from the University of Southern California School of Medicine in 1977. Pet'r's Ex. 14 at 1, ECF No. 40-1. She completed a residency in obstetrics and gynecology in 1981 and a fellowship in integrative medicine between 2010 and 2012. *Id.* Dr. Gersh has practiced in gynecology and integrative women's health care since 1981. *Id.* She has been certified by the American Board of Obstetrics and Gynecology since 1984. *Id.*

D. Respondent's Expert, Dr. Thomas Günter 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 2, ECF No. 56-3. 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.* Dr. Forsthuber has been a Professor of Immunology in the University of Texas at San Antonio's Department of Biology since 2005. *Id.* at 2–3. He is also an Adjunct Professor of Pathology and of Microbiology & 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 eighty-five articles and four book chapters as well as numerous abstracts. *Id.* at 19–27, 32–40. Much of Dr. Forsthuber's research is focused on autoimmunity and related topics. *See id.*

E. Respondent's Expert, Dr. David Frankfurter, M.D.

Dr. Frankfurter received his medical degree from Yale University in 1991. Resp't's Ex. D at 1, ECF No. 57-2. Following his medical degree, Dr. Frankfurter completed a residency in obstetrics and gynecology and a fellowship in reproductive endocrinology at Yale University and Harvard University, respectively. Resp't's Ex. C at 1, ECF No. 57-1. Dr. Frankfurter practices as a "Board Certified Reproductive Endocrinologist." *Id.* He currently serves as the Division Director of Reproductive Endocrinology, Fertility, and IVF and as Professor of Obstetrics and Gynecology at The George Washington University. *Id.* He has twenty years of experience treating women with POI. *Id.* A "significant proportion of [his] practice is comprised of women with diminished ovarian reserve (DOR) or POI." *Id.* He has published on and "developed therapeutic protocols aimed at" these conditions and patients. *Id.* He has "reviewed multiple trials involving women with POI[]" in his capacity as a member of the National Institutes of Child Health and Human Development (NICHD) Intramural Institutional Review Board (IRB). *Id.* He is an author of various articles, abstracts, book chapters, and presentations. Resp't's Ex. D at 5–13.

F. Respondent's Expert, Dr. Robert A. Yokel, Ph.D.

Dr. Yokel received his B.S. degree in pharmacy at the University of Wisconsin in 1968 and his Ph.D. in pharmacology at the University of Minnesota in 1973. Resp't's Ex. E at 1, ECF No. 58-1; Resp't's Ex. F at 1, ECF No. 58-2. He completed post-doctoral research at Concordia University in Canada. Resp't's Ex. F at 2. Dr. Yokel has been a member of the faculty at the University of Kentucky's College of Pharmacy since 1979 and has been a full Professor of Pharmacology and Toxicology since 1993. *Id.* Dr. Yokel began researching "the pharmacokinetics

and effects (pharmacodynamics) of aluminum" in 1979. Resp't's Ex. E at 1. He has "received nine major research grant awards from the United States National Institutes of Health (NIH) and Environmental Protection Agency (EPA) to conduct research on aluminum[.]" *Id.* He is an author of "approximately 150 peer-reviewed publications, over half [of which] focus on aluminum and/or its chelation." *Id.*; Resp't's Ex. F at 38–49.

III. Analysis

I find that Petitioners who are able to establish by a preponderant standard that their POI is autoimmune in nature have presented a sound and reliable causation theory pursuant to *Althen* prong one. Thus, I begin this analysis with a discussion of how autoimmune POI is identified. Next, I discuss the various theories Petitioners have proposed. Although Petitioners' hypotheses pertaining to adjuvants do not aid them in satisfying prong one, Petitioners have, through their explanation of the cross-reaction between specific proteins necessary for ovarian function and viral proteins, presented a sound and reliable medical theory.

A. POI Diagnosis and Etiology

As a factual predicate to proving vaccine-causation, it is each petitioner's burden to demonstrate by a preponderant standard that she actually suffers from the injury alleged to have been caused by her HPV 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) (finding that in a case where the injury itself is in dispute, it is appropriate for the special master to "first determine which injury was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury."). The Vaccine Act provides that a treating physician's diagnosis "shall not be binding on the special master or court," but that the special master should consider the "entire record and the course of the injury" when evaluating how much weight to afford a treating physician's diagnosis. 42 U.S.C. § 300aa-13(b)(1). In these cases, each petitioner must show by preponderant evidence that she suffers from POI. *See Broekelschen*, 618 F.3d at 1349; *see also Lombardi*, 656 F.3d at 1353.

POI is defined as amenorrhea[11] that lasts more than four months in women younger than 40. Pet'r's Ex. 26 at 1, ECF No. 42-9.[12] The amenorrhea is accompanied by a "hypoestrogenic-hypergonadotropic serum profile (follicle stimulating hormone ("FSH")[13] levels [greater than] 40

[11] Amenorrhea is "absence or abnormal stoppage of the menses[.]" *Amenorrhea*, DORLAND'S, https://www.dorlandsonline.com (last visited June 11, 2021).

[12] Mahbod Ebrahimi et al., *The role of autoimmunity in premature ovarian failure*, IRAN J. REPROD. MED. 13(8):461–472 (2015).

[13] The follicular stimulating hormone 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 . . . ." *Follicle-stimulating hormone*, DORLAND'S, https://www.dorlandsonline.com (last visited June 11, 2021). Ovarian follicles are "oocyte[s] and [their] encasing (follicular) cells, at any stage of development." *Ovarian follicle*, DORLAND'S, https://www.dorlandsonline.com (last visited June 11, 2021). Oocytes are "the immature female

mlU/mL on two occasions)." *Id.* Other clinical symptoms include "hot flushes and night sweats[], sleep disturbances[,] and dyspareunia[14] related to vaginal dryness." Pet'r's Ex. 25 at 3, ECF No. 42-8.[15] POI is a rare disease affecting "0.3-1% of [the] general population [ ]." Pet'r's Ex. 26 at 1. It is even rarer among young women, with an incidence rate of "0.01% of women under age 20 [and] 0.1% of women under age 30[.]" Pet'r's Ex. 13 at 1, ECF No. 39-3.[16] A significant number of patients have cases classified as idiopathic, but known causes include: "chromosomal/genetic abnormalities, metabolic/enzymatic factors, autoimmunity, infections, environmental toxins, and iatrogenic influences[.]" Pet'r's Ex. 26 at 1. Furthermore, "[t]he exact mechanism in pathophysiology of this disorder remains obscure[.]" *Id.* at 2. An ovarian biopsy is the definitive procedure for diagnosis, however it is "not recommended due to unknown clinical value, expense[,] and risks [ ]." *Id.* at 7.

There is some dispute regarding the prevalence of autoimmune POI, with studies that report it constitutes between 4% to 30% of all POI cases. *See* Pet'r's Ex. 13 at 2; Pet'r's Ex. 25 at 2; Pet'r's Ex. 26 at 2. Autoimmune cases can be hard to identify because "there is no clinically proven sensitive and specific serum test to confirm the diagnosis . . . ." Pet'r's Ex. 26 at 1. Autoimmune POI has traditionally been characterized by "the presence of lymphocytic oophoritis,[17] autoantibodies[18] to ovarian antigens, and associated autoimmune disorders." Pet'r's Ex. 25 at 2. Lymphocytic oophoritis is characterized by "[c]ellular infiltration of follicles by macrophages,[19] natural killer cells T-lymphocytes,[20] plasma cells,[21] and B-lymphocytes[.][22]" Pet'r's Ex. 26 at 4. While "[g]irls and young women who have POI on the basis of autoimmune lymphocytic

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reproductive cell[s] prior to fertilization[.]" *Oocyte*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[14] Dyspareunia refers to "difficult or painful sexual intercourse." *Dyspareunia*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[15] Jana Petríková and Ivica Lazúrová, *Ovarian failure and polycystic ovary syndrome*, AUTOIMMUNITY REVIEWS 11(6–7):A471–A478 (2012).

[16] Catherine M. Gordon et al., *Update on primary ovarian insufficiency in adolescents*, CURR. OPIN. PEDIATR. 27(4):511–19 (2015).

[17] Lymphocytes are "any of the mononuclear, nonphagocytic leukocytes [also known as white blood cells], found in the blood, lymph, and lymphoid tissues, that are the body's immunologically competent cells and their precursors." *Lymphocyte*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021); *Leukocyte*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). Oophoritis is "inflammation of an ovary." *Oophoritis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[18] Autoantibodies are "antibod[ies] formed in response to, and reacting against, a self antigen (i.e., one of the individual's own normal tissue constituents)." *Autoantibody*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[19] Macrophages are "any of the many forms of mononuclear phagocytes found in tissues." *Macrophage*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[20] T lymphocytes are "the cells primarily responsible for cell-mediated immunity[,]" which "are characterized by specific surface antigens[.]" *T Lymphocytes*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[21] Plasma cells are "terminally differentiated cell[s] of the B-lymphocyte lineage that produce[] antibodies[.]" *Plasma Cell*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[22] B lymphocytes are "the cells primarily responsible for humoral immunity, the precursors of antibody-producing cells (plasma cells)." *B Lymphocytes*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

oophoritis test positive for serum antiadrenal antibodies," in general, "[a]ntiovarian antibodies . . . are too nonspecific to be of use in identifying which patients have an autoimmune mechanism." Pet'r's Ex. 13 at 4. In cases where oophoritis is apparent, the "follicular depletion is the final stage of autoimmune attack," but "the size of the involved ovaries could [remain] normal or [become] enlarged on sonographic view." Pet'r's Ex. 26 at 4. One process to identify an autoimmune etiology of POI includes, "testing for the presence of 21-hydroxylase autoantibodies as an indicator for autoimmune lymphocytic oophoritis related to steroidogenic[23] cell autoimmunity." Pet'r's Ex. 13 at 2.

In addition to lymphocytic oophoritis, "antibodies binding to the various steroid hormone-producing cells [ ], gonadotropins and their receptors [ ], zona pellucida[24] [ ], oocyte [ ], corpus luteum[25] [ ], and several other antibodies such as anticardiolipin[26] and antinuclear[27] antibodies [ ] have been reported as the markers of ovarian autoimmunity." Pet'r's Ex. 26 at 2. Without identifying specific antiovarian autoantibodies, the research points to "antibodies directed against steroid-producing cells of various endocrine glands such as adrenal cortex[28] cells, . . . and theca cells[29] of the ovary . . . ." Pet'r's Ex. 26 at 2. The main targets of steroid cell antibodies are also present in autoimmune diseases with POI comorbidity. As a result, these diseases, including autoimmune polyendocrine syndromes[30] and Addison's disease,[31] can also be effective predictors of autoimmune POI.

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[23] Steroidogenic means "producing or giving rise to steroids[,]" which are "any of a group of lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system [and] include progesterone, adrenocortical hormones, sex hormones, [etc.]" *Steroidogenic*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021); *Steroid*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[24] Also known as the "pellucid zone[,]" the zona pellucida is "a thick, transparent, noncellular layer or envelope of uniform thickness surrounding an oocyte[.]" *Zona Pellucida*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[25] The corpus lutem, or yellow body of ovary, is "a yellow glandular mass in the ovary formed by an ovarian follicle that has matured and discharged its oocyte." *Corpus luteum*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[26] Anticardiolipin antibodies are "directed against cardiolipin[,]" which is a "phospholipid occurring primarily in mitochondrial inner membranes and in bacterial plasma membranes." *Anticardiolipin antibody*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021); *Cardiolipin*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[27] Antinuclear antibodies are "antibodies directed against nuclear antigens[.]" *Antinuclear antibodies*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[28] The adrenal cortex is "the outer firm yellowish layer that comprises the larger part of the suprarenal gland," which "secretes . . . many steroid hormones." *Cortex Glandulae Suprarenalis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). The suprarenal, or adrenal, gland is "a flattened endocrine gland found in the retroperitoneal tissues at the superior pole of the kidney." *Glandula Suprarenalis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[29] Theca cells are "cells of the theca interna and theca externa that surround developing ovarian follicles." *Theca Cells*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[30] Autoimmune polyendocrine syndromes, or polyendocrine autoimmune syndromes, are "syndromes comprising combinations of endocrine and nonendocrine autoimmune diseases." *Polyendocrine Autoimmune Syndromes*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[31] Addison disease is "a chronic type of adrenocortical insufficiency, characterized by hypotension, weight loss, anorexia, weakness, and a bronze like hyperpigmentation of the skin[]" that "is due to

Petitioner's expert, Dr. Shoenfeld, writes that studies on the reliability of using specific antiovarian antibodies to predict autoimmune POI are inconsistent. Pet'r's Ex. 17 at 7. Therefore, he notes that some authors advocate against relying "exclusively on the presence or absence of [antiovarian antibodies]" to determine the pathogenesis of any particular case of POI. *Id.* He opines that the "multiplicity of the suspected auto antigens and related antibodies illustrates the variety of pathological autoimmune processes that can cause ovarian damage." *Id.* However, he does note the "positive correlation between the presence of autoimmune oophoritis and serum adrenal cortex antibodies" in individuals suffering from POI. *Id.* at 8.

Respondent's expert, Dr. Forsthuber, identifies "three scenarios when autoimmune POI is presumed by clinicians [ ]: (1) POI associated with adrenal autoimmune disease (i.e. autoimmune Addison's disease); (2) POI associated with non-adrenal autoimmune diseases (e.g. autoimmune thyroid disease); [and] (3) [c]ases of isolated, idiopathic POI." Resp't's Ex. A at 2–3. Despite conflicting evidence about which autoantibodies are markers for autoimmune POI, Dr. Forsthuber notes that steroid-cell autoantibodies ("StCA") are the most frequently reported in this context. *Id.* at 3. Of these StCAs, Dr. Forsthuber identifies two that are expressed in the ovaries, and a third, 21-hydroxylase, that is only expressed in the adrenal cortex, but has "the highest diagnostic sensitivity for autoimmune POI [ ]." *Id.* He continues that "only women that are positive for StCAs show histopathological evidence of autoimmune infiltration of the ovaries (autoimmune oophoritis) on biopsy [ ]." *Id.* Despite this definitive language, Dr. Forsthuber then concedes that if said autoantibodies "are not present in women with POI, autoimmune oophoritis is typically not found on ovarian biopsy, even in woman that present with other autoimmune diseases, such as autoimmune thyroiditis[32] [ ]." *Id.* Dr. Forsthuber's use of the word "typically" suggests there may be atypical cases that do not fit his conclusion.

In his report, Dr. Forsthuber notes that the majority (60%) of POI patients have "enlarged, multicystic ovaries," but normal or small ovaries can be found in a significant minority of cases, 33% and 7% respectively. *Id.* at 4. He continues that "[a]utoimmune cell infiltration of the ovary, i.e.[,] autoimmune oophoritis, is essentially only observed when POI is associated with [Addison's disease], but is absent when POI occurs in combination with other autoimmune diseases . . . ." *Id.* at 5. Dr. Forsthuber entertains the hypothesis "that in autoimmune POI associated with [Addison's disease], the theca cells of the ovary may be attacked by the autoimmune response because they express the antigens targeted by StCA in ovaries and adrenal glands . . . and because of infiltration of lymphocytes around these cells [ ]." *Id.* While he does not reject outright this possibility, Dr. Forsthuber restates that the process by which "immune tolerance to steroid cells enzymes in the ovaries may be broken in POI and autoantibodies and autoimmune inflammation of the ovaries induced has remained unresolved." *Id.* Dr. Forsthuber also presents the possibility that these "autoantibodies arose secondarily due to tissue damage, and [ ] may therefore represent an epiphenomenon [without] pathogenic function." *Id.* He is unable to provide an opinion on the underlying mechanisms of POI cases "presumed to be of an autoimmune etiology because of their association with autoimmune disease conditions other than [Addison's disease.]" *Id.* at 6. He notes

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tuberculosis- or autoimmune-induced destruction of the adrenal cortex . . . ." *Addison Disease*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). Adrenocortical insufficiency refers to "abnormally diminished secretion of corticosteroids by the suprarenal (adrenal) cortex." *Adrenocortical Insufficiency*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[32] Thyroiditis refers to "inflammation of the thyroid gland[.]" *Thyroiditis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

that "convincing evidence or probable disease mechanism[s] are lacking[ ]" to show an autoimmune etiology in these cases where there is no evidence of autoantibodies and autoimmune inflammation. *Id.* Dr. Forsthuber suggests that these cases "may [actually] be due to the hormonal and/or other metabolic disturbances created by autoimmune thyroiditis . . . or due to other genetic or environmental factors." *Id.*

While acknowledging that "[i]mportant insights into the mechanisms promoting human autoimmune diseases have come from experimental animal models[,]" Dr. Forsthuber remains skeptical of the use of animal models to determine an autoimmune etiology for POI. *See id.* at 6–7. He argues that these studies are "limited by the lack of spontaneous disease models . . . ." *Id.* The studies have revealed that "disease in most of these models is primarily mediated by cellular immunity, i.e.[,] $CD4^+$ T cells[.][33]" *Id.* at 7. Furthermore, "[a]utoantibodies against ovarian antigens [have] develop[ed] in some of these models, . . . after immunization with inhibin-[alpha] peptide,[34]" and this can lead to a premature primordial follicle depletion. *Id.* This appears to be a clear and logical autoimmune pathology, but Dr. Forsthuber notes that unlike in some animals, "the primordial follicle pool is preserved for a long period in [human] POI patients [ ]." *Id.* Dr. Forsthuber uses this difference as support for his argument that animal studies cannot be used as a basis for establishing autoimmune etiology in humans. *See id.*

Both Drs. Shoenfeld and Forsthuber agree that autoimmune POI has traditionally been diagnosed in association with autoimmune antibodies, oophoritis, and autoimmune disease comorbidity. Dr. Frankfurter, however, cautions that this evidence of POI must be evaluated in the context of adrenal insufficiency. Resp't's Ex. C at 7, ECF No. 57-1. Dr. Frankfurter asserts that "[m]aking this conclusion outside of [this context] is not practical and no longer routinely pursued." *Id.* In support of this contention, he notes that diagnosing oophoritis requires sectioning the entire ovary, lest the areas of inflammation are missed. *Id.* He also reiterates that antiovarian antibody testing lacks sufficient specificity and sensitivity to be definitive. *Id.* Lastly, he notes that without an inciting event, "the chronology of POI relative to other autoimmune conditions is highly variable." *Id.* Therefore, he concludes, "the relative frequency of clear autoimmune POI remains small." *Id.*

Dr. Frankfurter has responded to Dr. Shoenfeld's theory as it relates to the autoimmune etiology of POI by characterizing it as speculative and overly broad. *See id.* at 7–8. He argues that "competing theories on the potential role of autoimmunity illustrate the lack of a unified theory or

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[33] CD4 cells are "T lymphocytes that carry the CD4 antigen; they are helper T cells." *CD4 Cells*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). CD antigens are "any of a number of cell surface markers, expressed by leukocytes and used to distinguish cell lineages, developmental stages, and functional subsets; [they] can be identified by specific monoclonal antibodies . . . ." *CD Antigen*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). Helper cells are "differentiated T lymphocytes whose cooperation [ ] is required for the production of antibody against most (T-dependent) antigens." *Helper Cells*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[34] Inhibin refers to "either of two glycoproteins, A and B, each composed of a common alpha subunit and one of two beta subunits; they are secreted by the gonads and found in seminal plasma and follicular fluid, and inhibit pituitary production of [FSH]." *Inhibin*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). A peptide is "any member of a class of compounds of low molecular weight that yield two or more amino acids on hydrolysis. They are the constituent parts of proteins . . . ." *Peptide*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

clear understanding of the process at hand." *Id.* at 8. Dr. Frankfurter further concludes that the presence of antibodies cannot be a marker for autoimmune POI "[b]ecause these antibodies are found in normal women and those without POI[; therefore,] it can be assumed that they may be present before the onset of POI." *Id.* Dr. Frankfurter refers to Dr. Shoenfeld's statement "that the exact mechanism of autoimmunity in the pathophysiology of [POI] remains obscure[,]" Pet'r's Ex. 17 at 7, and opines that without a "valid and clinically appropriate test . . . (excluding that associated with the adrenal gland), it is difficult to conclude that a case is autoimmune in nature versus of unexplained etiology." Resp't's Ex. C at 9.

Dr. Frankfurter makes clear that his expectation for each petitioner is that she provide definitive proof of an autoimmune etiology for POI. Petitioners, however, are under no obligation to meet this standard. Instead, each petitioner must show it is more likely than not that she suffers from POI with an autoimmune etiology. In cases where there is evidence of lymphocytic oophoritis, adrenal or ovarian autoantibodies, and comorbid autoimmune disorders, I will presume the POI is autoimmune in nature. If all three of these factors are not present, a petitioner may still be able to establish it more-likely-than-not that her POI is autoimmune, given her particular medical history. If, for example, a petitioner has another autoimmune disorder associated with POI such as Addison's disease, along with anti-ovarian antibodies, that may be sufficient. Other more common characteristics of a systemic immune reaction, such as inflammation, prolonged fever, and fatigue, may also be considered with other POI symptoms to assess if an individual diagnosis is autoimmune. If a petitioner's clinical presentation is not at all consistent with a POI etiology, i.e., there is no evidence of oophoritis or anti-steroid antibodies, it is unlikely that she will be able to show how her POI could be characterized as autoimmune in nature. The presence of autoimmune co-morbidities without other factors will not be sufficient to meet the more likely than not autoimmune etiology. The causation theories that the petitioners have presented all rely on a pathogenic immune response to vaccination. Therefore, a POI diagnosis with an autoimmune etiology is a necessary condition for further analysis pursuant to *Althen*. *See Hibbard*, 698 F.3d at 1365 (determining that a petitioner's "failure to show that she had autonomic neuropathy would be fatal to her case[]" when that injury "was a necessary component of her theory of vaccine–induced injury[]"). Each petitioner should take care to evaluate whether it is reasonable to assert an autoimmune POI in light of her specific medical history. The factors for consideration will not be re-litigated nor expanded absent advances in the research.

B. Althen Prong One

Under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question: "can the vaccine[] at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Hum. Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *mot. for rev. denied*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548–49. A petitioner is not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge[] the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano,* 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). However, as the Federal Circuit has made clear, "simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d

1334, 1339 (Fed. Cir. 2014) (citing *Moberly*, 592 F.3d at 1322). Rather, "[a] petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case." *Moberly*, 592 F.3d at 1322. In general, "the statutory standard of preponderance of the evidence requires a petitioner to demonstrate that the vaccine more likely than not caused the condition alleged." *LaLonde*, 746 F.3d at 1339.

Here, Dr. Shoenfeld proposes several different theories. For purposes of organization, his theories that involve the adjuvant (aluminum) in the vaccine will be discussed first. Then, his theory involving the viral components of the vaccine will be evaluated.

i. Adjuvant / Aluminum-Based Theories

In his reports, Dr. Shoenfeld presents multiple mechanisms to explain how the HPV vaccine can cause POI. While known for his Autoimmune Syndrome Induced by Adjuvants ("ASIA") theory, Dr. Shoenfeld does not refer to this theory here. Instead, he explains that "the presence of an adjuvant in conjunction with the vaccine can greatly increase the innate immune response to the antigen by augmenting the activity of dendritic cells[35] [ ], lymphocytes, and macrophages by mimicking natural infection." Pet'r's Ex. 17 at 8. He writes that the "[a]djuvants [added to the HPV vaccine] accomplish this task by mimicking specific sets of evolutionarily conserved molecules . . . ." *Id.*

This theory could still be described as an autoimmune syndrome induced by adjuvants, but unlike his traditional ASIA theory, here potential causes of the pathogenic immune response are identified. His argument suggests that pathogenic cross-reactivity between components of the HPV vaccine and the female reproductive system occurs because a molecular mimic is in the adjuvant. He is combining molecular mimicry with an adjuvant-induced injury and lists "liposomes,[36] LPSs,[37] molecular cages for antigens, components of bacterial cell walls, and endocytosed nucleic acids[38]" as examples of potential mimicked molecules. *Id.*

Although Dr. Shoenfeld did not present his ASIA theory in this case, the role of the aluminum adjuvant in his adjuvant-induced, molecular mimicry hypothesis is quite similar to his trademark theory in its reliance on adjuvants for a pathogenic immune response. He developed ASIA for several types of vaccine injuries and has tried without success to establish that this phenomenon, often in conjunction with molecular mimicry, can result in various autoimmune diseases. In fact, the validity of the ASIA theory has been repeatedly called into doubt in the

[35] Dendritic cells are "a heterogeneous group of antigen-presenting cells derived from myeloid precursors that have numerous branching processes[.]" *Dendritic Cells*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).
[36] Liposomes are "spherical particle[s] in an aqueous medium, formed by a lipid bilayer enclosing an aqueous compartment." *Liposome*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).
[37] An LPS, or lipopolysaccharide, is "a complex of lipid and polysaccharide [that is] is a major component of the cell wall of gram-negative bacteria, a type of endotoxin and important group-specific antigen (O antigen)." *Lipopolysaccharide*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).
[38] Endocytosis is "the uptake by a cell of material from the environment by invagination of its plasma membrane[.]" *Endocytosis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021). A nucleic acid is "a high-molecular-weight nucleotide polymer[,]" such as DNA or RNA. *Nucleic Acid*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

Program. *See D'Angiolini v. Sec'y of Health & Hum. Servs.*, 122 Fed. Cl. 86, 102 (2015) (upholding the special master's "determin[ation] that ASIA does not provide[] a biologically plausible theory for recovery"), *aff'd*, 645 Fed. Appx. 1002 (Fed. Cir. 2016); *Garner v. Sec'y of Health & Hum. Servs.*, No. 15–063V, 2017 WL 1713184, at *8 (Fed. Cl. Spec. Mstr. Mar. 24, 2017) (observing that the ASIA theory "is, at a minimum, incomplete and preliminary—and therefore unreliable from an evidentiary standpoint"); *Rowan v. Sec'y of Health & Hum. Servs.*, No. 10–272V, 2014 WL 7465661, at *12 (Fed. Cl. Spec. Mstr. Dec. 8, 2014) (rejecting the ASIA theory because it "is not a proven theory" and no "persuasive or reliable evidence" supports it); *Johnson v. Sec'y of Health & Hum. Servs.*, No. 10–578V, 2016 WL 4917548, at *7–9 (Fed. Cl. Spec. Mstr. Aug. 18, 2016) (rejecting Dr. Shoenfeld's expansive medical theory that "any adjuvant [is] capable of causing any autoimmune disease," finding it "overbroad, generalized, and vague, to the point that it could apply to virtually everyone in the world who received a vaccine containing an adjuvant and then at some time in their lives developed an autoimmune disease."). The primary reason for ASIA's rejection is its "changing and imprecise" diagnostic criteria, which are unable to "distinguish between afflicted and un-afflicted patients." *D'Angiolini*, 122 Fed. Cl. at 102.

Dr. Shoenfeld's proposed theory here suffers from flaws similar to his ASIA theory. If, as Dr. Shoenfeld asserts, the cross-reactivity occurs between a biological system and the aluminum adjuvant, this theory could be applied to any adjuvanted vaccine and body system with homologous peptide chains consisting of five or six amino acids. Dr. Frankfurter argues that "[t]here are hundreds of human proteins that contain [one or more of the homologous penta-peptide[39] chains] in question." Resp't's Ex. L at 7, ECF No. 78-1. Dr. Frankfurter reasoned that "given the short sequence[s] identified by Dr. Shoenfeld [are] found in many other proteins within the human proteome, if an autoimmune attack targeted the penta-peptide in question, one would expect, a patient to experience consequences beyond isolated POI." *Id.*

A second mechanism Dr. Shoenfeld discusses is disruption in ovarian cyclicity as the result of ovo-toxicity. Dr. Shoenfeld notes that women are born "with a finite number of undeveloped, primordial follicles that cannot be further generated after birth." Pet'r's Ex. 17 at 9. He continues that the number of viable follicles that any one woman possesses may be affected by environmental or occupational chemicals. *Id.* Dr. Shoenfeld writes that "[a] number of studies have shown that exposure to direct ovarian toxicants often leads to destruction of oocytes and POI." *Id.* Dr. Shoenfeld discusses "[c]hemicals that selectively damage large growing or antral follicles[40] only temporarily interrupt reproductive function because these follicles can be replaced by recruitment from the pool of primordial follicles." *Id.* He writes, "chemicals that destroy oocytes contained in primordial and primary follicles often lead to permanent infertility and [POI], because once a primordial follicle is destroyed, it cannot be replaced." *Id.* Consequently, Dr. Shoenfeld cautions that vaccine components "must be examined for the [possible components that may cause] ovarian toxicity." *Id.* at 12. He specifically includes "both adjuvants, used to enhance the immune reaction,

[39] A pentapeptide is "a polypeptide containing five amino acids." *Pentapeptide*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[40] Antral follicles, or tertiary ovarian follicles or vesicular ovarian follicles, are "growing ovarian follicle[s] comprising a primary oocyte surrounded by multiple layers of follicular cells and containing a fluid-filled vesicle [.]" *Tertiary Ovarian Follicle*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

and in the case of most vaccines involves an aluminum adjuvant, as well as various 'excipients', [i.e.,] emulsifiers and other sunstances [sic] for solubilization and stabilization of the vaccine." *Id.*

Dr. Shoenfeld asserts that "[a]luminum has long been recognized as a neurotoxin[.]" *Id.* at 13. He does not, however, provide any evidence that "aluminum's inherent neurotoxic and immunotoxic properties [that] are well known in the medical literature" had any negative effects when used in Gardasil vaccine trials or as an adjuvant. *Id.* In fact, the studies that Dr. Shoenfeld relies on note that "few studies focused on the potential immunological responses induced by Al [aluminum]." Pet'r's Ex. 37 at 1, ECF No. 43-10.[41] While there is evidence that a "[h]igh Al dose or long time Al exposure will make humans and animals exert toxic effect[,]" *id.* at 2, Dr. Shoenfeld was unable to provide support that a one-time, limited aluminum exposure through vaccination will also lead to the development of reproductive dysfunction, cognitive deficiency, or immune disease. Special masters have previously concluded that evidence of adverse effects from chronic exposure to a substance does not constitute evidence of adverse effects from a single exposure to that substance. *See Spahn v. Sec'y of Health & Hum. Servs.*, No. 09-386V, 2014 WL 12721080, at *17 (Fed. Cl. Spec. Mstr. Sept. 11, 2014) (determining that evidence that chronic or repeated exposures to mercury could cause tics or other issues was not evidence that a one-time mercury exposure through vaccination could cause tics), *aff'd*, 133 Fed. Cl. 588, 603 (2017). Dr. Shoenfeld was also unable to provide any studies that show that aluminum is an ovary toxin in humans. One mouse study submitted by Dr. Shoenfeld, wherein the animals were administered drinking water with aluminum for four months, showed the rats suffered from "a drop in serum levels of estrogen, progestogen, and testosterone, and the pituitary hormones LH and FSH." Pet'r's Ex. 17 at 15 (citing Pet'r's Ex. 42, ECF No. 44-5[42]). Another study showed that subchronic exposure of aluminum "was shown to disrupt the structure of the [rat] ovary." *Id.* (citing Pet'r's Ex. 43, ECF No. 44-6[43]). In mammal studies, it is clear that chronic, prolonged exposure is needed for these pathological effects. A study done on hamster ovary cells also "revealed a dose-related cytotoxic effect on both ovarian structure and size . . . ." *Id.* at 16 (citing Pet'r's Ex. 45, ECF No. 44-8[44]). Dr. Forsthuber responds to these models by pointing out that Dr. Shoenfeld relies on studies that require repeated exposure to aluminum, "without specifying how much or how many doses are required." Resp't's Ex. A at 16. Dr. Forsthuber notes that even Dr. Shoenfeld stated that "repeated exposure to the 'toxin' is often required[.]" *Id.*

Dr. Shoenfeld also submitted a study that hypothesized that exposure to aluminum may affect cognitive function. *See* Pet'r's Ex. 39 at 1, ECF No. 44-2.[45] However, that study identified "metal inert gas welders" and "people accidentally exposed to drinking aluminum sulfate-contaminated water" as likely sufferers. *Id.* at 7. These individuals endure chronic exposure in higher doses than

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[41] Y.Z. Zhu et al., *Impact of aluminum exposure on the immune system: A mini review*, ENV'T TOXICOLOGY & PHARMACOLOGY 35:82–87 (2013).
[42] Nan Wang et al., *Effects of Subchronic Aluminum Exposure on the Reproductive Function in Female Rats*, BIOL. TRACE ELEM. RES. 145:382–87 (2012).
[43] Fu Y et al., *Effects of sub-chronic aluminum chloride exposure on rat ovaries*, LIFE SCI. 100(1):61–66 (2014).
[44] AL Di Virgillo et al., *Comparative study of the cytotoxic and genotoxic effects of titanium oxide and aluminum oxide nanoparticles in Chinese hamster ovary (CHO-K1) cells*, J. HAZARD. MATER., 177(1–3):711–18 (2010).
[45] Maryline Couette et al., *Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction*, J. OF INORGANIC BIOCHEMISTRY 103:1571–78 (2009).

one would expect from the Gardasil vaccine. One case study that contemplated an association between macrophage myofasciitis[46] and aluminum exposure focused on a man whose "[o]pen muscle biopsy of the [vaccination] site three years later revealed the presence of aluminum hydroxide[,]" but there is nothing in the article that explores a causal connection between the vaccination as the significant cause of aluminum exposure and the development of disease. *See generally* Pet'r's Ex. 39. It is unclear how Dr. Shoenfeld relies so heavily on chronic exposure as analogous to a limited, one-time exposure during vaccination. Furthermore, the human studies do not relate back to ovarian injury or even reproductive dysfunction. At best, these studies call for additional studies, and Dr. Shoenfeld's own writings criticize the medical and research community for a refusal to adequately study aluminum adjuvants. Given the limited, one-time exposure to aluminum at the time of vaccination, these studies do not provide strong support for Dr. Shoenfeld's ovo-toxicity theory.

Despite Dr. Shoenfeld's criticisms, "[the World Health Organization] and Global Advisory Committee on Vaccine Safety [ ] have stated that there is 'no evidence of a health risk from aluminum-containing vaccines[.]" Resp't's Ex. A at 17 (citing http://www.who.int/vaccine_safety/committee/topics/aluminum/questions/en/). Dr. Forsthuber also notes that aluminum "is ubiquitous in the environment," including in foods and health products, and "is present at substantial levels in healthy individuals and distributed throughout the body and in every organ." *Id.* It is unclear how Dr. Shoenfeld would ever be able to make the case that the relatively small, isolated "amount of aluminum that could hypothetically be absorbed by vaccination with the HPV vaccine has the toxic effects [he] claim[s.]" *Id.*

Dr. Forsthuber describes Dr. Shoenfeld's assertions regarding the role of adjuvants in the induction of autoimmune disease as "concepts or theories" that are "really nothing that can be learned from, commented on, or discussed." *Id.* at 15. He follows these strong allegations by making the point that although "[a]luminum adjuvants induce local inflammatory reactions[,] . . . they have little systemic effects, and in fact, reduce systemic adverse reactions." *Id.* More "[i]mportantly," Dr. Forsthuber argues "a number of studies showed that antibody production after vaccination with adjuvanted vaccine remained specific for the vaccine antigens and did not induce autoantibodies [ ]." *Id.* at 15–16 (citing Resp't's Ex. A, Tab 5, ECF No. 53-6;[47] Resp't's Ex. A, Tab 20, ECF No. 55-1[48]). He concludes that even with a much stronger adjuvant, complete Freund's adjuvant[49] "autoimmune pathology of the ovaries could not be induced in [a] model of

[46] Myofasciitis is "inflammation of a muscle and its fascia, particularly of the fascial insertion of muscle to bone." *Myofasciitis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).
[47] Gianfranco Di Genova et al., *Vaccination of human subjects expands both specific and bystander memory T cells but antibody production remains vaccine specific*, BLOOD 107(7): 2806–13 (2006).
[48] F. Eun-Hyung Lee et al., *Circulating human antibody-secreting cells during vaccinations and respiratory viral infections are characterized by high specificity and lack of bystander effect*, J. OF IMMUNOLOGY, 186(9): 5514–21 (2011).
[49] A complete Freund adjuvant is "a water-in-oil emulsion incorporating antigen . . . The addition of killed, dried mycobacteria . . . to the oil phase . . . elicits cell-mediated immunity (delayed hypersensitivity), as well as humoral antibody formation." *Freund Adjuvant*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

experimental autoimmune oophoritis" in the absence of ovarian autoantigen. *Id.* at 16 (citing Resp't's Ex. A, Tab 1, ECF No. 53-2[50]).

Petitioners ultimately do not focus on adjuvant-induced toxicity or adjuvant molecular mimics to establish causation. Dr. Shoenfeld has been unable to identify any human studies that directly support these theories centered around adjuvants. There is also the difficulty of conducting a study on a condition that is often discovered in an individual several years post any relevant vaccination. Studies are not required to establish causation in the Program, and I will not hold the lack of studies against Petitioners here. However, Petitioners are required to provide more than speculation that short, unidentified, homologous peptide sequences between the aluminum adjuvant in the HPV vaccine and various parts of female reproductive and endocrine systems necessarily mean pathogenic cross-reaction. Plainly put, the causation theory must be applicable to the specific vaccine and injury in question. Dr. Shoenfeld has not persuasively responded to the concern that his adjuvant-based theories are simply vague conjecture applicable to any adjuvanted vaccine followed by autoimmune disease, regardless of the amount of time that passed between vaccination and injury.

I do not find that Petitioners have established by a preponderant standard that the HPV vaccine can cause POI via adjuvant-induced autoimmunity solely, or in conjunction with any other mechanism that focuses on an aluminum adjuvant, including ovo-toxicity. Petitioners have not developed either of those arguments outside of vague assertions and have narrowed their causation theory significantly in subsequent filings.

ii. Viral Component Cross-Reaction

Indeed, Petitioners ultimately focus on the cross-reaction between specific proteins necessary for ovarian function and viral proteins. Dr. Shoenfeld explains that molecular mimicry is hypothesized to occur when "a susceptible host acquires an infection or gets vaccinated with an agent that has antigens that are immunologically similar to the host antigens but differ sufficiently to induce an immune response when presented to T cells." Pet'r's Ex. 17 at 2. He continues that this causes "the host's tolerance to its own antigens [to] break[] down[,] and the host mounts an attack on its own tissue, mistaking it for a foreign substance that needs to be neutralized. This is termed a 'cross-reaction[.]'" *Id.* Petitioners argue that "[a]ll four of the HPV strains contained in Gardasil share homology or mimic human proteins associated with ovarian function." Pet'r's Br. at 4, ECF No. 86. Petitioners assert that "molecular mimicry [occurs] between L1 proteins contained in Gardasil and proteins essential to proper ovarian function, [and] antibodies produced in response to the four L1 proteins cross[-]react[] with these proteins resulting in binding or damage to those proteins." *Id.* Citing medical literature, Petitioners note that "ATM [ataxia telangiectasia] is an enzyme that helps a cell repair DNA damage [ ]" and mutations. *Id.* at 8 (citing Pet'r's Ex. 81, ECF No. 74-1;[51] Pet'r's Ex.106, ECF No. 85-1[52]). They continue that the resulting

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[50] Cengiz Z. Altuntas et al., *Autoimmune Targeted Disruption of the Pituitary-Ovarian Axis Causes Premature Ovarian Failure*, J. OF IMMUNOLOGY 177(3): 1988–96 (2006).

[51] Carrolee Barlow et al., *Atm deficiency results in severe meiotic disruption as early as leptonema of prophase I*, DEVELOPMENT 125:4007–17 (1998).

[52] Elena J. Tucker et al., *Premature Ovarian Insufficiency: New Perspectives on Genetic Cause and Phenotypic Spectrum*, ENDOCRINE REVIEWS 37(6):609–35 (2016).

dysfunctional proteins, have been associated with the development of POI." Pet'r's Br. at 8. This could, therefore, be the protein that cross-reacts in a specific case to cause autoimmune POI. Furthermore, Dr. Shoenfeld asserts that "Gardasil contains molecular mimics for sixteen (16) proteins that relate to the function of the ovaries." *Id.* Dr. Shoenfeld identifies many of these proteins, including: ATM (serine-protein kinase that is involved in oocytes degeneration, infertility); ATS (disintegrin metalloproteinase with thrombospondin motifs – an ovulatory protein that correlates with oocyte fertilization capacity); and EGFR (epidermal growth factor receptor essential for the production of matured and developmentally competent oocytes). Pet'r's Ex. 80 at 2–3, ECF No. 73-1. Dr. Shoenfeld also identifies four other proteins with homologous peptides from at least three strains of HPV, although their specific functions are not described. *See id.* at 2. Petitioners argue this alone "should be enough." Pet'r's Br. at 9. Petitioners also note that "in another case[,] there may be autoantibodies to the adrenal glands, which would add an additional piece to [their] medical theory." *Id.*

Respondent's experts agree that the proteins identified by Dr. Shoenfeld contain peptide chains that also appear in HPV. Dr. Frankfurter notes that some of the proteins relate to newborn low birth weight and intrauterine growth restrictions. *See* Resp't's Ex. L at 6. Dr. Frankfurter points out that POI "preclude[s] pregnancy[;]" therefore, any theory including proteins that relate to these conditions "is without biological basis, and considering them in the context of the current discussion creates a distraction." *Id.* Dr. Forsthuber also questions the relevance of peptides shared between HPV and human proteins that are not specifically related to oocyte function. *See* Resp't's Ex. K at 3, ECF No. 77.

While Dr. Shoenfeld identified some proteins that are present in more pertinent proteins, both of Respondent's experts remain critical of Dr. Shoenfeld's theory. Dr. Forsthuber goes on to note that one amino acid sequence that Dr. Shoenfeld identified "is present in 425 human, animal, and microbial proteins[.]" *Id.* Indeed, "essentially all of the other amino acid sequences claimed by Dr. Shoenfeld as relevant for ovarian dysfunction are also found in other human proteins." *Id.* at 4.

Dr. Frankfurter notes Dr. Shoenfeld is very selective in his "reporting [of] the full breadth of human and non-human (bacterial, fungal, and viral) proteins that share the searched penta-peptide sequence[s]" he identifies. Resp't's Ex. L at 7. These short sequences, Dr. Frankfurter explains, lack specificity "and it should not be surprising that proteins with reproductive function would be among those that contain [these] amino acid sequence[s]. *Id.* Due to the presence of these sequences in so many other bodily systems, Dr. Frankfurter again argues that if the sequences were material to the function of a specific bodily system or organ, "one would expect a patient to experience consequences beyond isolated POI." *Id.*

Dr. Frankfurter also criticizes the claim that the peptides identified by Dr. Shoenfeld can lead to ovarian dysfunction when "mutated or improperly functioning[.]" *Id.* He explains that "immunogenicity[, or how effectively an antigen provokes an immune response] is not specific to a tissue, but rather a particular epitope[, which is the part of the antigen that the immune system recognizes]." *Id.* Dr. Frankfurter continues that if Dr. Shoenfeld's theory was correct, "immune targeting should lead to phenotypic features seen in gene mutation syndromes involving the same target protein." *Id.* Because autoimmune tissue damage does not manifest in the same way as genetic mutation, Dr. Frankfurter reasons that the homologous peptides identified by Dr. Shoenfeld

and "expressed in multiple tissues" cannot cross-react and result in pathogenesis "just in one organ system." *Id.*

Dr. Frankfurter concedes that "patients with ATM mutations manifest ovarian failure[.]" *Id.* at 8. He continues, however, that "they also demonstrate an unstable gait, progressive motor degeneration and telangectasias[53] [sic] [ ]." *Id.* Dr. Frankfurter is skeptical that Dr. Shoenfeld's theory is sound without a requirement of other symptoms consistent with "the known phenotype seen with that particular gene mutation." *Id.* Indeed, a case wherein a petitioner is exhibiting these additional symptoms would provide strong evidence of the applicability of Dr. Shoenfeld's theory in that instance.

All of the Petitioners alleging vaccine-caused POI are young adults and some were children at the time of diagnosis. Dr. Frankfurter argues that he does not believe cross-reactivity with ATM would cause POI in a child or young adult. *See id.* While conceding that ATM "affect[s] the progression of prophase I[54] prior to oocyte arrest in meiosis I[55] and lead[s] to oocyte degeneration prior to birth[,]" he notes that "meiosis I arrest occurs in utero during fetal development[and] well before HPV vaccination [ ]." *Id.* Dr. Frankfurter is "not aware of evidence on the influence of ATM on egg development post[-]natally and how that would affect egg function or number." *Id.* Put plainly, he argues that any effect this type of cross-reaction would have must occur prior to the birth of a petitioner while ATM is still active. Respondent did not submit evidence that ATM was limited to its role in oocyte development, and it has not been asserted that ATM's function has been completely identified and understood.

Respondent submitted a study by Naleway et al. [56] which acknowledged that there had been some "[c]oncern about a potential association between HPV and POI" within the medical community due to case reports. Resp't's Ex. J at 6, ECF No. 72-1. However, the Naleway study "found no evidence of increased risk of POI after HPV vaccination[.]" *Id.* Notwithstanding their ultimate conclusion, the researchers went on to explain that the often-extended temporal relationship between symptom onset and diagnosis and the difficulty in accurately identifying POI makes, "[s]tudying POI as a vaccine adverse event [ ] challenging[.]" *Id.* at 5–6. The researchers cautioned that "this study was underpowered to detect small increases in POI risk associated with vaccination." *Id.* at 5.

Dr. Shoenfeld responds to the Naleway study with an article by Dr. Gayle DeLong.[57] Dr. Shoenfeld argues that Dr. DeLong's article supports his contention that women have become

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[53] A telangiectasia is a "permanent dilation of preexisting small blood vessels . . . to form focal, discolored lesions, usually in the skin or mucous membranes." *Telangiectasia*, DORLAND'S, https://www.dorlandsonline.com (last visited June 15, 2021).

[54] Prophase is "the first stage in cell reduplication[,]" which "consists of five stages[]" in meiosis I. *Prophase*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[55] Meiosis is "a special type of cell division occurring in the maturation of germ cells . . . During meiosis I, homologous chromones are paired and segregated . . . ." *Meiosis*, DORLAND'S, https://www.dorlandsonline.com (last visited June 14, 2021).

[56] Allison L. Naleway et al., *Primary Ovarian Insufficiency and Adolescent Vaccination*, PEDIATRICS 142(3) (2018).

[57] Gayle DeLong, *A lowered probability of pregnancy in females in the USA aged 25–29 who received a human papillomavirus vaccine injection*, J. OF TOXICOLOGY AND ENV'T HEALTH, Part A, 81:14, 661–74 (2018).

increasingly infertile since the development and widespread administration of the human papillomavirus vaccine. *See* Pet'r's Ex. 80 at 1. Dr. DeLong argues that "[d]ata suggest[s] that the HPV vaccine is associated with a lower probability of having been pregnant." Pet'r's Ex. 79 at 13, ECF No. 63-1. Dr. DeLong, however, has no medical background. She is an economist. *See id.* at 2. Furthermore, her findings do not control for contraception use or other medical, professional, or personal considerations of modern women. She oversimplifies the reproduction rates and conflates the decrease in pregnancy and childbirth with infertility. Dr. Shoenfeld builds on her conclusions and implicitly argues that if able, every woman would choose to have children at the same rate as previous generations, despite the fact that modern women have alternative professional and personal opportunities that may not have been available in the past. The refusal to acknowledge the potential impact of changes in female reproductive medicine or economic circumstances, and other alternative causes before making a determination of causation with respect to Dr. DeLong's work, undercuts Dr. Shoenfeld's opinions regarding causation here. He recognizes that association is not causation but seems to rely almost entirely on association to establish causation regarding the infertility of women in the general population. As I have noted in the past, I do not find Dr. DeLong's work to be applicable to identifying a vaccine-caused injury. *See Decker v. Sec'y of Health & Hum. Servs.*, No. 15-17V, 2020 WL 7889059, at *33 (Fed. Cl. Spec. Mstr. Dec. 14, 2020). I do not find that her methodology is sound, nor are the conclusions Dr. Shoenfeld draws from her articles reasoned. Her article holds little to no probative value and will be weighed accordingly.

Dr. Shoenfeld also asserts that the Naleway researchers had a conflict of interest because they were paid by vaccine manufacturers. Pet'r's Ex. 80 at 1. He notes that Naleway is "a single center study." *Id.* Additionally, Dr. Shoenfeld takes issue with the follow-up reviews done on select patients and criticized the clinical adjusters for potentially "second guess[ing] a treating physician's diagnosis of POI." *Id.* He argues that "a massive peptide sharing exists between Gardasil HPV L1s peptides and human proteins" related to ovarian failure and other forms of reproductive dysfunction. *Id.* at 2. Among those peptides, Petitioners focus specifically on "serine-protein kinase ATM [that Dr. Shoenfeld states] is involved in oocytes degeneration[.]" *Id.* In his final report, Dr. Shoenfeld identifies several other peptide chains with a "powerful immunologic impact and the highest cross[-]reactivity risk . . . when considering that a penta[-]peptide acts as a minimal determinant in humoral and cellular immune recognition [ ]." *Id.* at 5.

Unlike with Petitioners' adjuvant-based causation theories presented here, and in other cases where Respondent is able to directly attack the cause and effect sequence of a petitioner's biological mechanism, *see Nunez v. Sec'y of Health & Hum. Servs.*, No. 14-863V, 2019 WL 2462667 (Fed. Cl. Spec. Mstr. Mar. 29, 2019); *Dougherty* v. *Sec'y of Health & Hum. Servs.*, No. 15-1333V, 2018 WL 3989519 (Fed. Cl. Spec. Mstr. July 5, 2018)**,** Respondent has not presented a persuasive rebuttal of the mechanical explanation of Petitioners' molecular mimicry theory. Dr. Forsthuber acknowledges that "[m]olecular mimicry between microbes and human self-antigens as the cause of human autoimmune diseases has been implicated as a potential mechanism of human autoimmune diseases." Resp't's Ex. A at 12. However, he notes that "to date, there are only very few examples of human autoimmune diseases that could be potentially attributed to molecular mimicry." *Id.* He then argues that because his "extensive literature search of PubMed has not revealed any evidence that autoimmune POI is linked to any particular microorganism, being it viral, bacterial, or fungal[,] . . . there is no evidence for a causative role of molecular mimicry in POI . . . ." *Id.*

Dr. Frankfurter argues that "[i]f Dr. Shoenfeld's theory were correct, [ ] people who have had HPV infections would be at heightened risk of POI for several years, whenever they received another vaccine or had another infection." Resp't's Ex. L at 6. Dr. Frankfurter explains this is "because during the course of an infection, the resultant tissue damage can create an almost limitless potential of small amino acid chains." *Id.* He continues that "[w]ith an HPV infection, viral shedding and tissue inflammation can last years, during which the immune response to HPV peptides/immunogens would be ongoing." *Id.* This person would also likely be exposed to annual vaccines, boosters, or "various natural phenomena like insect bites, common scrapes/wounds, . . . all of which would induce a heightened immune response and therefore serve to facilitate the mimicry response." *Id.* Despite this logical sequence, Dr. Frankfurter notes that "there is no evidence that people with HPV are at heightened risk of developing POI, or any autoimmune disease." *Id.* He concludes that without a corresponding increase in POI among women who suffer from HPV, it is not likely that the vaccine is causative. *See id.* The pervasiveness of HPV in the general population is further evidence, according to Dr. Frankfurter, of the unlikelihood of Petitioners' theory. *See id.*

Respondent is over relying on the rarity of the event underlying Petitioners' theory to deem it unlikely. Petitioners have established by a preponderant standard that POI can be autoimmune. In those instances, molecular mimicry can occur if there is an immune response triggered by vaccination, and homology between peptides in the reproductive system specifically relating to ovarian function and components of the vaccine. This can lead to cross-reaction, and it is logical that the production of autoantibodies, particularly in an individual already susceptible due to autoimmune comorbidities, could lead to the development of autoimmune POI. Dr. Shoenfeld has identified several proteins that contain short peptide chains that play a role in oocyte development and function. Respondent's experts counter that these peptide chains are too short to be material. They argue that these sequences are seen in many other pathogens, as well as throughout the body, and the medical community has not seen the wide-spread triggering of other types of organ-specific autoimmune disease when individuals are exposed to said pathogens. All of the experts agree, however, that POI is multi-factorial, and there are many opportunities for cross-reactions between multiple homologous peptide chains within the same individual. It is probable that a specific combination of vaccination history, predisposition to autoimmune disease, and cross-reaction with several sequences in multiple specific proteins can precipitate this rare event. If the exact mechanism and progression of all autoimmune diseases had been discovered, we would have better luck predicting, treating, and curing these diseases, even within families. Our inability to account for the somewhat random nature and extreme rarity of a disease like autoimmune POI should not be an insurmountable hurdle for a logical theory that affirmatively answers the question: "can the vaccine at issue cause the type of injury alleged?" A plausible theory of causation is not enough, but scientific certainty as established through epidemiology is too much to require.

The presence of presumed vaccine-caused injuries on the Program's Table that are believed to be the result of molecular mimicry provides a potential analogous baseline plausibility for all other autoimmune illnesses. However, it is not enough to simply assert that a petitioner has an autoimmune disease and molecular mimicry is the mechanism. At that point, a theory is, as Respondent argues here, simply speculation. It also cannot be enough that a medical expert can simply identify homologous peptides from a generic BLAST search that are not, in any way, linked to the biological process that is dysfunctional or has suffered injury. The line must be drawn somewhere between speculation and certainty. Here, Petitioners identified cross-reaction between

components of the vaccine and proteins in the body that are directly responsible for the health and productivity of the organ at issue. Respondent is requiring an additional step and insisting on direct, testable evidence of pathology. Respondent is also looking for a statistically significant rise in the disease, despite its rarity, and an explanation for why only the ovary would be targeted, despite the opportunity for cross reactivity in "almost every second human protein that shares at least one 5-amino acid sequence with [a strain of] HPV[.]" Resp't's Ex. K at 9. That is a step too far to establish a right to entitlement here.

In cases where a petitioner can establish by a preponderant standard that her POI diagnosis is autoimmune, Petitioners will have detailed a causation theory that is sound and reliable pursuant to *Althen* prong one. It is true that a penta-peptide chain is undisputedly short. However, given the multifactorial pathogenesis of POI, I find it logical that cross-reactions between multiple, short peptides within proteins relevant to oocyte function and in HPV vaccines may produce an ovary-specific autoimmune attack. Other factors helpful in determining the applicability of this theory to any specific case include an appropriate temporal relationship, the types of autoantibodies produced by a petitioner, adjacent symptoms, and comorbidities.

Although I find Dr. Shoenfeld presents a theory I believe is sound and reliable, I do not expect it to be applicable to every case submitted. Indeed, these are rare effects, and that will hold true even within the Program. Petitioners are still expected to establish it more likely than not that they suffer from autoimmune POI and that Dr. Shoenfeld's theory is applicable to each of them. They must also provide preponderant evidence that molecular mimicry did occur and that there exists a temporal relationship between vaccination and injury. Each petitioner's medical record should be analyzed to see if her claim can proceed to *Althen* prongs two and three in accordance with this Ruling.

IV. Conclusion

The petitioners in the above-mentioned cases have presented a causation theory that, while not applicable to all of them, does survive *Althen* prong one under specific circumstances. In instances where a petitioner can establish by a preponderant standard that she suffers from autoimmune POI, the case should continue to a determination of whether the causation theory presented is applicable to said petitioner based on her specific medical history. A petitioner whose condition does not present evidence of an autoimmune etiology, such as lymphocytic oophoritis, adrenal or ovarian autoantibodies, and comorbid autoimmune disorders, will not be able to establish that the causation theory presented here is applicable to her claim. There 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. Petitioners should proceed with the prosecution of their claims in accordance with this Ruling.

IT IS SO ORDERED.

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