In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 24, 2023

AUTUMN ORM,	*	PUBLISHED
Petitioner,	*	No. 14-257V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Human Papillomavirus ("HPV") Vaccine; Celiac Disease.
Respondent.	*	

Mark Theodore Sadaka, Law Offices of Sadaka Associates, LLC, Englewood, NJ, for Petitioner.
Debra A. Filteau Begley, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On April 2, 2014, Autumn Orm ("Petitioner")[2] filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The petition was originally filed by Theodore and Jodi Orm, as parents of Autumn Orm. Petition (ECF No. 1). On November 9, 2015, the case caption was amended to Autumn Orm because she reached the age of majority. Order dated Nov. 9, 2015 (ECF No. 60).

et seq. (2012)[3] alleging that as a result of human papillomavirus ("HPV") vaccines (Gardasil) she received on August 30, 2011 and November 22, 2011, she suffers from celiac disease.[4] Amended ("Am.") Petition at Preamble (ECF No. 172); Joint Submission, filed May 23, 2022, at 1 (ECF No. 296).

After carefully analyzing and weighing the evidence presented in this case, in accordance with the applicable legal standards, the undersigned finds Petitioner has failed to provide preponderant evidence that the HPV vaccines she received caused her to develop celiac disease. Thus, Petitioner has failed to satisfy her burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Therefore, the petition must be dismissed.

II. ISSUES TO BE DECIDED

The parties agree that Petitioner suffers from celiac disease but disagree as to the onset of her illness. Joint Submission at 1. They also disagree about whether the HPV vaccinations can or did cause Petitioner's celiac disease[5] and dispute all three Althen prongs. Id.

III. PROCEDURAL HISTORY

This case has a lengthy procedural history. Petitioner initially alleged that she suffered bilateral leg weakness and myasthenia gravis as a result of her HPV vaccinations. Petition at Preamble (ECF No. 1). Subsequently, she filed an amended petition, in which she alleged that she suffered "numerous autoimmune diseases including: Celiac Disease, Postural Orthostatic Tachycardia Syndrome ("POTS"), Chronic Fatigue Syndrome ("CFS"), Small Fiber Neuropathy, in addition to others," which she alleged were caused by her HPV vaccinations on August 30, 2011 and November 22, 2011. Am. Petition at Preamble.

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

[4] Petitioner initially alleged that she suffered from bilateral leg weakness and myasthenia gravis, and subsequently asserted that she suffered from celiac disease, Postural Orthostatic Tachycardia Syndrome ("POTS"), Chronic Fatigue Syndrome ("CFS"), Small Fiber Neuropathy, and other autoimmune diseases. Petition at Preamble (ECF No. 1); Amended ("Am.") Petition at Preamble (ECF No. 172). In her joint submission, however, Petitioner narrowed the issues and confirmed celiac disease as her alleged vaccine-related illness. Joint Submission, filed May 23, 2022, at 1 (ECF No. 296).

[5] In her supportive brief, Petitioner took the position that "the development of celiac disease as a result of Gardasil [HPV vaccine] led to the development of additional autoimmune disease." Petitioner's Brief ("Pet. Br."), filed May 7, 2021, at 6 (ECF No. 265). Since the undersigned finds that Petitioner has failed to prove causation by preponderant evidence, she does not reach the question of whether Petitioner's celiac disease caused or contributed to other illnesses.

The parties filed numerous expert reports and medical literature during the course of litigation. This case was assigned to the undersigned on December 8, 2021. Notice of Reassignment dated Dec. 8, 2021 (ECF No. 285). Subsequently, the parties filed a joint submission to clarify Petitioner's vaccine-related injury. Joint Submission. During a status conference on June 8, 2022, the undersigned asked the parties to consider settlement negotiations. Order dated June 8, 2022, at 1 (ECF No. 297). On July 1, 2022, Petitioner filed a status report stating her preference to "resolve this case through a ruling on the record." Petitioner's ("Pet.") Joint Status Report ("Rept."), filed July 1, 2022 (ECF No. 300). Subsequently, in a status report dated November 10, 2022, Respondent "reviewed [P]etitioner's demand and determined that he would like to continue with litigation." Respondent's ("Resp.") Status Rept., filed Nov. 10, 2022 (ECF No. 309). Respondent also requested that the undersigned issue a ruling on the record. Id.

This matter is now ripe for adjudication.

IV. MEDICAL TERMINOLOGY[6]

Celiac disease is "a life-long autoimmune condition mainly involving the proximal small intestine of genetically susceptible individuals." Pet. Exhibit ("Ex.") 88 at 14. Gluten, defined as a "storage protein of wheat," along with similar proteins in barley and rye, are the "offending inducers" of the illness. Id. "Tissue transglutaminase (tTg)[7] is the auto-antigen against which the abnormal immune response is directed [] and the [immunoglobulin A ("IgA")]-anti-tTg is the most used serological marker[] to diagnose the disease." Id. Iron deficiency anemia, caused by nutritional deficiency, is a known complication of the illness. Id. Historically, the "classic picture" of celiac disease included the triad of malnutrition, chronic diarrhea, and abdominal pain. Id.

The disease is triggered by ingestion of gluten, a protein present in wheat, and other grains such as barley and rye. Resp. Ex. T at 4. When a person with celiac disease eats gluten, the protein in it damages the surface of the intestine, or the villi, which are "small finger-like projections along the wall of the small intestine." Id. When the villi are damaged, the intestine is unable to absorb nutrients when eating. Id. This may cause malnourishment, weight loss, diarrhea, bleeding, and abdominal pain. Id. Other symptoms of celiac disease may include anemia, rash, headaches, fatigue, bone and joint pain, osteoporosis, mouth ulcers, and heartburn. Id.

Diagnosis is made by obtaining blood tests, including anti-tTG antibody and anti-endomysial antibody ("EMA") testing, as well as endoscopy with biopsy to determine whether

[6] The medical terminology is taken from expert reports submitted by Petitioner's expert, Dr. Aaron Lerner, and Respondent's expert, Dr. Chris A. Liacouras. See Pet. Exhibit ("Ex.") 88; Resp. Ex. T.

[7] In some medical records, expert reports, and medical articles, this antibody is also abbreviated as TTG. The undersigned will use the abbreviation tTG throughout this Decision.

abnormalities of the lining of the intestine, as described above, exist. Resp. Ex. T at 4. Treatment is adherence to a life-time gluten-free diet. Id.

V. FACTUAL SUMMARY

A. Summary of Medical Records[8]

Petitioner was born on November 4, 1997. Pet. Ex. 1. Her medical history prior to the vaccinations at issue is unremarkable. Pet. Ex. 12 at 5-11. At her well-child visit to her pediatrician on November 1, 2010, she was assessed as a well child, although she was noted to have scoliosis. Id. at 4. At that visit, Petitioner received influenza and hepatitis A vaccinations. Id. at 55; Pet. Ex. 2 at 2. There is no evidence of any adverse reaction to those vaccinations.

On August 30, 2011, Petitioner saw her primary care doctor, Dr. Paula Dekeyser, D.O., for an evaluation of hip pain, specifically over the iliac crest, that occurred while running. Pet. Ex. 12 at 2. Dr. Dekeyser's history notes that Petitioner was in cross-country, and "ha[d] been running a lot since the first part of August . . . [and] has felt pain in her hips." Id. Assessment was "bilateral iliac crest pain, probably musculoskeletal." Id. (emphasis omitted). Petitioner received her first HPV vaccine at that visit. Id. Petitioner received her second HPV vaccine on November 22, 2011. Id. at 1.

Moving forward to 2012, on January 5, 2012, Petitioner presented to Dr. Dekeyser with "shortness of breath" that occurred during exercise "for a couple months," which made it "very difficult" for her to participate in cross-country and basketball. Pet. Ex. 14 at 3. During her last basketball game, she had "burning in her chest." Id. She also complained of diarrhea, "intermittent abdominal pain," and weight loss. Id. On physical examination, Petitioner appeared very pale and she had some abdominal tenderness. Id. Complete blood count ("CBC") revealed "profound anemia at 8.7."[9] Id.

A referral was made to gastroenterologist, Dr. Sachin S. Kunde, who Petitioner saw on January 10, 2012. Pet. Ex. 4 at 17; Pet. Ex. 65 at 14. Dr. Kunde's history stated,

> [Petitioner] is a 14-year-old . . . who presents here with chronic diarrhea, weight loss, and anemia. [Petitioner] was healthy until the summer of 2011, when she started noticing tiredness. She started cross-country running and she started feeling very tired even when she was not running at that time. Later, this was followed by loss of weight. She has lost approximately 6 pounds of weight in the last 2 months. She started noticing that she was having loose stools in the last 2 to 3 months. . . . She generally gets upper crampy abdominal pain in the middle of

[8] Petitioner filed numerous medical records, many of which relate to other diagnoses and medical care that is not related to the diagnosis of, or care and treatment of, her celiac disease. For the sake of clarity and brevity, this medical summary covers only Petitioner's care and treatment related to celiac disease.

[9] Petitioner's hemoglobin was 8.7 gm/dL (normal range 12.0-14.5 gm/dL). Pet. Ex. 12 at 20.

> the night and she has to go to the bathroom. She has never seen blood in the stool, but her workup . . . showed . . . anemia. She does not have any joint pain, but she complains of her bones aching.

Pet. Ex. 4 at 19. Family history was significant for Crohn's disease[10] and gastrointestinal disease. Id. at 17.

Laboratory studies revealed positive Hemoccult tests.[11] Pet. Ex. 4 at 19; Pet. Ex. 12 at 18. Hemoglobin had decreased to 7.7 "at the lowest." Pet. Ex. 4 at 19; see also Pet. Ex. 12 at 18. Petitioner's mean corpuscular volume ("MCV")[12] was low at 66.5 (normal range 79.9-92.3 fL). Pet. Ex. 12 at 15. Petitioner also had decreased iron levels at 9 (normal range 40-150 mcg/dl) and low ferritin[13] at 2.7 (normal range 11-307 ng/mL). Pet. Ex. 4 at 19; Pet. Ex. 12 at 16. The positive Hemoccult tests, indicating blood in the stool, along with weight loss, tiredness, and iron deficiency due to blood loss, led Dr. Kunde to consider differential diagnosis of infectious or inflammatory colitis, specifically Crohn's disease. Pet. Ex. 4 at 19. Additional diagnostic tests were ordered, including upper endoscopy and colonoscopy. Id. Petitioner was also referred to hematology. Id.

Laboratory studies performed on January 11, 2012 were significant for an elevated tTG IgA antibody of 150 (normal < 19 U/mL).[14] Pet. Ex. 4 at 11. Endoscopy and colonoscopy done

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[10] Crohn's disease is an inflammatory bowel disease of the gastrointestinal tract. Crohn Disease, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=70226 (last visited Feb. 23, 2023).

[11] Hemoccult, or guaiac test, tests for occult blood, which is "blood present in such small quantities that it is not visible to the naked eye and can be detected only by chemical tests of suspected material," such as feces. Hemoccult, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=21983 (last visited Feb. 23, 2023); Occult Blood, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=60877 (last visited Feb. 23, 2023).

[12] Mean corpuscular volume ("MCV") is "the average volume of erythrocytes," which are "elements found in peripheral blood." Mean Corpuscular Volume, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=118634 (last visited Feb. 23, 2023); Erythrocyte, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=17213 (last visited Feb. 23, 2023).

[13] Ferritin is a "form[] in which iron is stored in the body." Ferritin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=18386 (last visited Feb. 23, 2023).

[14] For a list of all of Petitioner's tTG results, see Pet. Ex. 88 at 13. EMA testing was recommended for further evaluation or for confirmation where clinically indicated. Pet. Ex. 4 at 11. However, the results of this testing, if done, do not appear to be in the records.

January 11, 2012 revealed numerous abnormalities including villous[15] alteration, focal active duodenitis, and erosion in the duodenum; mild chronic gastritis in the stomach; mild focal active colitis in the cecum; and focal active colitis in the ascending, transverse, descending, and rectal sigmoid colon.[16] Id. at 13. The pathologist noted that "[i]n the absence of an infectious etiology, inflammatory bowel disease [was] a consideration, although the biopsies [did] not show marked chronic injury." Id. Microscopic examination showed the following:

> A. Duodenal mucosa features severe villous alteration and effacement with mild intraepithehal lymphocytosis. The lamina propria contains a dense lymphoplasmacytic infiltrate. Eosinophils are increased at 20-50+ per high power field. Neutrophils are sprinkled throughout and are active in the surface epithelium and focally forming active cryptitis without crypt abscesses. Granulomas or parasites are not identified. There is crypt hyperplasia. There is some crypt distortion.
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> B. Gastric antral and fundic type mucosa features relatively intact foveolar and glandular epithelium. The lamina propria contains a light lymphoplasmocytic infiltrate. Eosinophils number less than 20 per high power field. In neutrophils are sparse, but focally active on one fragment. Granulomas are not identified. Helicobacter pylori type organisms are not identified on routine stain; a properly controlled immunohistochemical stain is negative.
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> C. Esophageal squamous mucosa features no significant basal cell hyperplasia or spongiosis. Lymphocytes are sparse.
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> D. Terminal ileum biopsies feature intact villous architecture with focal prominent lymphoid nodularity. The lamina propria contains the usual mixture of lymphocytes and plasma cells with eosinophils increased at 20-60 per high power field. Significant neutrophilic inflammation or granulomas are not identified.
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> E.-1. Cecal, colonic, and rectosigmoid biopsies are similar and feature relatively intact surface epithelium with minimal crypt distortion. The lamina propria contains the usual mixture of inflammatory cells. Eosinophilia is prominent at 50+ per high power field. All of the biopsies feature some degree of focal active cryptitis without crypt abscesses or granulomas.

Id. at 15.

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[15] Villous means "shaggy with soft hairs; covered with villi." Villose, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=53144 (last visited Feb. 23, 2023).

[16] For a discussion of biopsy changes seen in celiac disease, see Pet. Ex. 103 at 2 (Hugh J. Freeman, Pearls and Pitfalls in the Diagnosis of Adult Celiac Disease, 22 Can. J. Gastroenterology 273 (2008)).

Dr. Kunde spoke with Petitioner's family about the pathology results and the positive tTG IgA antibody results and diagnosed Petitioner with celiac disease on January 16, 2012. Pet. Ex. 65 at 39. Follow-up blood work showed improved hemoglobin (12.1). Id. at 41. On February 22, 2012, the hemoglobin and iron results showed continued improvement, and the plan was to continue a gluten-free diet and iron supplements. Id. at 50. Petitioner continued to have follow-up lab studies, and in April 2012, her hemoglobin was normal at 12.3. Id. at 56. Her ferritin remained low at 10. Id.

On July 25, 2012, Petitioner's mother call Dr. Kunde's office reporting that Petitioner had shortness of breath, leg pains, and extreme lack of energy for one week. Pet. Ex. 65 at 67. Labs showed that her iron level was less than 10 (low). Id. Additional lab studies were ordered. Id. In a follow-up call on August 3, 2012, Petitioner's mother explained that Petitioner was "tired, exhausted, [and] depressed." Id. at 63. Due to participation in sports, and travel for sports, Petitioner was eating at fast food restaurants and having "a very difficult time with her [celiac disease diagnosis]." Id. Petitioner's mother also expressed concerns that Petitioner had depression and was interested in a support group or counseling. Id. Information was provided to the family, and a social worker was contacted to assist with these concerns. Id. at 62. On August 3, 2012, Petitioner's tTG IgA was elevated, and Dr. Kunde opined that Petitioner's celiac disease was "not controlled well." Id. at 63.

Labs drawn September 4, 2012 showed normal hemoglobin (12.8) and iron (88.00) levels and an elevated tTG IgA (9.8; normal < 4.0 U/mL). Pet. Ex. 9 at 21-22; Pet. Ex. 65 at 91-92. Petitioner and her family met with a registered dietician on October 11, 2012, for education on gluten-free diet. Pet. Ex. 65 at 101. Petitioner continued to have difficulty with her gluten-free diet while traveling for sports. Id. She saw Dr. Kunde's nurse practitioner for a follow-up on October 11, 2012. Id. At that visit, Petitioner reported that she was taking her iron supplement, following a gluten-free diet, playing basketball, and running track. Id. at 101-02. She reported abdominal symptoms only with gluten ingestion. Id. at 102. On December 20, 2012, Petitioner's tTG IgA result was "improved and near normal" at 5.9. Id. at 123-25; see also Pet. Ex. 9 at 26. Dr. Kunde planned to repeat testing in six months. Pet. Ex. 65 at 125.

Dr. Dekeyser saw Petitioner for follow-up on February 11, 2013. Pet. Ex. 5 at 125. Petitioner complained of "pain in her upper legs, over quad[riceps] and [shortness of breath] with exertion. Her total [iron] was 39 down from 85 in December." Pet. Ex. 65 at 127. On February 14, 2013, Petitioner's labs revealed positive antinuclear antibodies ("ANA")[17] at 1:640. Pet. Ex. 5 at 152. Dr. Kunde spoke with Petitioner's mother on February 20, 2013 to report that the tTG IgA was "mildly elevated but improved compared to [time of] diagnosis (150 vs. 31)." Pet. Ex. 65 at 142. The other labs, iron and hemoglobin, were normal. Id. Dr. Kunde recommended stool studies, and if positive, they would consider endoscopy studies. Id. Petitioner's stool

[17] Antinuclear antibodies ("ANA") are "antibodies directed against nuclear antigens; ones against a variety of different antigens are almost invariably found in systemic lupus erythematosus and are frequently found in rheumatoid arthritis, scleroderma (systemic sclerosis), Sjögren syndrome, and mixed connective tissue disease." Antinuclear Antibodies, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=56804 (last visited Feb. 23, 2023). For a list of all of Petitioner's ANA results, see Pet. Ex. 88 at 13.

studies were negative (did not show bleeding) but she continued to have diarrhea, and was weak and short of breath on exertion. Id. at 143. Dr. Kunde recommended endoscopy and colonoscopy. Id.

In 2013 and 2014, Petitioner underwent extensive diagnostic testing and treatment with intravenous immune globulin ("IVIG") infusions for ongoing issues with weakness and she saw numerous specialists, including neurology, neuromuscular, psychiatry, cardiology, pulmonology, and genetics, at the University of Michigan. See Pet. Exs. 149(a)-(c). These specialists did not provide specific care or treatment relative to Petitioner's celiac disease.

In 2017, Petitioner was seen by immunologist, Dr. Jill Schofield. See Pet. Ex. 202. On August 30, 2017, Petitioner's tTG IgA level was 7 (normal range 0-3), interpreted as weakly positive. Id. at 22. Dr. Schofield noted that "[t]here [was] suspicion that [Petitioner] [was] being exposed to hidden sources of gluten given persistently positive anti-[tTG]." Id. at 29.

On December 19, 2019, now age 22, Petitioner saw Dr. Michael David Rice at the Michigan Medicine Gastroenterology Clinic to establish care for her celiac disease. Pet. Ex. 335 at 9, 11. She reported a past medical history of "antiphospholipid antibody syndrome, Sjogren syndrome, [POTS], mast cell activation syndrome, history of [pulmonary embolus] on chronic anticoagulation therapy, and celiac disease." Id. at 11. Petitioner reported that she kept a gluten-free diet and since doing so, "many of her symptoms significantly improved." Id. at 12. Dr. Rice recommended updated labs, endoscopy and colonoscopy studies, and a referral to nutrition services. Id. at 16-17. Blood work revealed Petitioner's tTG IgA was 66 (normal < 15 U/mL). Id. at 52. Her iron level was low and oral iron replacement was recommended. Id. at 77. Computerized tomography ("CT") showed a "few prominent thickened loops of proximal small bowel/jejunum," consistent with her history of celiac disease. Id. at 67. Upper endoscopy and colonoscopy performed on February 25, 2020 revealed no abnormalities. Id. at 106-07. Biopsies taken during these studies were also normal. Id. at 167. Capsule endoscopy done the same date showed normal small bowel and no changes to suggest that she had complications from her celiac disease. Id. at 142-43.

Follow-up with Dr. Rice occurred virtually on May 13, 2020. Pet. Ex. 335 at 176. She reported being more vigilant with her gluten-free diet and her bowel movement pattern had improved. Id. Follow-up was recommended in six months. Id. at 182. Petitioner's virtual visit with Dr. Rice was scheduled for January 28, 2021, however, it is not clear from the records whether Dr. Rice saw Petitioner for that appointment. Id. at 194-97.

No additional records related to Petitioner's celiac disease have been filed.

B. Hearing Testimony, Declarations, and Affidavits[18]

1. Affidavit and Testimony of Petitioner[19]

Petitioner executed an affidavit on September 12, 2016, at the age of 18, describing her participation in sports from 2010 through 2013. Pet. Ex. 60. She explained that in the eighth grade, from August 2010 to June 2011, she ran cross-country and track and played basketball. Id. at ¶¶ 3-4. During this school year, she did not have any physical conditions that affected her ability to play at her "maximum ability." Id. at ¶ 6. This remained true for the summer of 2011. Id. at ¶ 8. On August 30, 2011, she received her first HPV vaccine. Id. at ¶ 10. After reviewing her medical records from that date, she recalled telling her doctor that she had hip pain while running. Id. (citing Pet. Ex. 66). Petitioner recalled that at a cross-country meet on September 10, 2011, she had "pain in both of [her] legs and [her] entire body was weak and [she] had difficulty breathing." Id. at ¶ 11. "This was the first time that [Petitioner] experienced anything like this." Id. After this, she continued to have similar problems during practices and meets. Id. at ¶ 14. She also developed "excruciating pain in [her] chest" as well as leg pain that occurred the last meet of her freshman year. Id. at ¶ 15. Petitioner continued to experience weakness, pain in her legs, difficulty breathing, and fatigue in November and December 2011. Id. at ¶¶ 16-18. During a basketball practice on December 29, 2011, Petitioner felt that she could not breathe, and "[her] lungs felt like they were 'on fire.'" Id. at ¶ 18. This event precipitated an appointment with Petitioner's physician, Dr. Dekeyser, on January 5, 2012. Id. at ¶ 20.

In addition to her affidavit, Petitioner also testified at a hearing in this matter on September 16, 2016. Transcript ("Tr.") 3. Her testimony was consistent with her affidavit, summarized above. She testified that she did not begin to have any physical problems until a cross-country meet on September 10, 2011. Tr. 29-30. On that date, she "could barely breathe," she felt "very weak," and her "legs were like achy, almost." Tr. 30-31. By the cross-country meet on October 15, 2011, Petitioner realized that "something was majorly wrong." Tr. 32. Her symptoms had increased, she "couldn't breathe," and she had "a burning sensation in [her] legs." Id. From that time until her second HPV vaccination, Petitioner experienced "major fatigue." Tr. 37.

Moving forward, Petitioner explained that on December 29, 2011, she had practice for varsity basketball. Tr. 41. Prior to practice, she had begun to notice that when she walked upstairs, she had shortness of breath, and she had begun "seeing like a fading in [] [her] eyes."

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[18] Several other exhibits were filed by Petitioner, including documents from her Facebook page from 2010 through 2013, and documents from her mother's Facebook page for the same period. See Pet. Exs. 51-59. Copies of emails between Petitioner's mother and Petitioner's physicians were filed. See Pet. Ex. 62. Various articles, including several about Petitioner, phone records, and basketball and track schedules, were also filed. See Pet. Exs. 72-76. The undersigned has reviewed these documents but did not find them relevant to the issues in dispute, and therefore, they are not summarized herein.

[19] Although Petitioner's affidavit covers 2010 until 2013, the undersigned summarizes only the portions relevant to the issue of onset of her celiac disease.

Id. During basketball practice, she was not able to keep up with the other players, and her "lungs were literally burning as if they were on fire, almost. It was worse than before" and she "could barely breathe." Id. She told her mother about her problems, and her mother made an appointment for Petitioner to see her physician, Dr. Dekeyser on January 5, 2012. Tr. 42, 44. After testing, Petitioner learned that she had celiac disease. Tr. 45.

2. Affidavit and Testimony of Petitioner's Mother, Jodi Orm

Petitioner's mother, Jodi Orm, executed an affidavit on April 7, 2014, describing the onset of her daughter's illness. She averred that Petitioner complained of "shortness of breath and weak legs" during cross-country meets on September 10, September 17, and October 4, 2011. Pet. Ex. 3 at ¶¶ 4-6. She further averred that Petitioner did not have these symptoms before she received the HPV vaccine on August 30, 2011. Id. at ¶ 16.

Ms. Orm filed another affidavit, executed September 12, 2016, in which she summarized the events that occurred relative to Petitioner's health beginning in the summer of 2011. Pet. Ex. 61. Notably, Ms. Orm has a Master of Science in Nursing and is a Nursing Education Consultant. Id. at ¶ 1. She averred that prior to September 2011, her daughter was healthy and a talented athlete who excelled at sports. Id. at ¶ 3. Although Petitioner had hip pain in August 2011, it was not viewed as a serious condition, but attributed to cross-country running. Id. at ¶ 5. Ms. Orm recalled that at the cross-country meet on September 10, 2011, Petitioner was out of breath and weak. Id. at ¶ 6. Petitioner complained of leg weakness and soreness, which continued throughout the season. Id. at ¶¶ 6-9. In early January 2012, Petitioner was diagnosed with iron deficiency and celiac disease. Id. at ¶ 12. The remainder of Ms. Orm's affidavit dealt with the course of Petitioner's celiac disease, as well as her work up for other medical conditions not relevant to the issues here.

Like Petitioner, Ms. Orm testified at the hearing on September 16, 2016, and her testimony was consistent with her affidavits. Ms. Orm testified about the September 10, 2011 meet and recalled that Petitioner said that her "legs felt weird" and she was "short of breath." Tr. 156. Ms. Orm also recalled the events of December 29, 2011, particularly that Petitioner was "sobbing" and "very short of breath." Tr. 159. Ms. Orm made an appointment for Petitioner to see Dr. Dekeyser. Tr. 160. Ultimately, they learned that Petitioner had iron deficiency and celiac disease. Tr. 161. Ms. Orm explained that she did not seek medical care for Petitioner in September 2011 when she had shortness of breath during the cross-country meet because the symptoms went away. Tr. 210. The symptoms were "milder in the beginning" and "episodic" and then they "would go away." Tr. 210-11.

3. Statements and Affidavits from Petitioner's Coaches[20]

Petitioner's former coach Mandi Johnson submitted an email on October 16, 2014 and an affidavit executed on July 19, 2016, describing the decline in Petitioner's performance during

[20] Petitioner's cross-country schedules for 2010 and 2011 and her basketball schedule for 2011-2012 were filed. See Pet. Ex. 47 (cross-country 2011); Pet. Ex. 49 (basketball); Pet. Ex. 50 (cross-country 2010).

track and basketball her freshman (2011-2012) and sophomore years (2012-2013) of high school as compared to prior years (2008-2010). Pet. Exs. 16, 41. Ms. Johnson specifically noticed that Petitioner was behind the other runners her freshman year. Pet. Ex. 16 at 1. When Petitioner began basketball that November, she was "very short winded" and was no longer one of the fastest players on the team. Id. Coach Johnson also described Petitioner's decline during the basketball season beginning in 2011 through the following season ending in 2013. Pet. Ex. 41 at ¶¶ 6-12.

Coach Doug Ingalls sent an email dated October 21, 2014 and executed an affidavit July 18, 2016 stating that in the seventh grade and summer basketball, from 2009 to the summer of 2010, Petitioner "could run all day." Pet. Ex. 17 at 1; see also Pet. Ex. 42 at ¶¶ 1-4. During this time frame, Petitioner never became tired during games and "had virtually, no physical limits." Pet. Ex. 42 at 1. He did not observe Petitioner during her freshman year (2011-2012). Pet. Ex. 17 at 1; Pet. Ex. 42 at ¶ 5. In her sophomore year (2012-2013), Mr. Ingalls was "shocked" when he saw that Petitioner could "only run or play 20 to 30 seconds at a time." Pet. Ex. 17 at 1; see also Pet. Ex. 42 at ¶ 5.

Coach Dorene Ingalls wrote a letter emailed on October 21, 2014 and executed an affidavit on July 18, 2016, describing the difference she observed in Petitioner's athletic abilities from elementary school through junior high and high school. Pet. Exs. 19, 43. Ms. Ingalls noted that Petitioner did not run well her freshman year (2011-2012), and when she began basketball, she was unable to participate in "more than a few minutes of intense workout." Pet. Ex. 19 at 2; see also Pet. Ex. 43 at ¶¶ 3-5.

Emily Fullerton, Petitioner's Physical Education teacher and cross-country coach, submitted an email October 19, 2014 as well as an affidavit executed July 19, 2016, with Petitioner's cross-country times from eighth grade (2010) and freshman year (2011). Pet. Exs. 18, 40. Coach Fullerton averred that in the fall of 2010, Petitioner excelled at cross-country, but in 2011, her pace decreased. Pet. Ex. 40 at ¶¶ 6-7, 10-11.[21] Coach Fullerton also noted that in the fall of 2011, Petitioner complained of "fatigue, sore legs[,] and lack of energy." Id. at ¶ 11.

[21] A spreadsheet of Petitioner's cross-country race times with key statistics was filed. See Pet. Ex. 86. Petitioner's 2010 average pace was 10:20:50 minutes/mile; her 2011 average pace was 10:59:38 minutes/mile; her pre-vaccine average pace was 10:27:35 minutes/mile; and her post-vaccine average pace was 11:04:58 minutes/mile. Id. at 1. These numbers differ from those provided by Coach Fullerton. The times referenced in Coach Fullerton's affidavit are likely incorrect. For example, Petitioner likely did not run a 9.01-minute mile for two miles. See Pet. Ex. 40 at ¶¶ 6-7.

VI. EXPERT OPINIONS[22]

A. Petitioner's Expert, Dr. Aaron Lerner[23]

1. Background and Qualifications

Dr. Lerner graduated from the Sackler School of Medicine, Tel-Aviv University in Israel in 1977. Pet. Ex. 87 at 2; Pet. Ex. 88 at 1. In 1984, he completed a pediatric gastroenterology and nutrition fellowship at Children's Hospital of Buffalo in New York. Pet. Ex. 87 at 4. He served as the head of pediatric gastroenterology and nutrition unit at the Carmel Medical Center in Haifa, Israel from 1988-1995, and again from 2005-2015. Pet. Ex. 88 at 1. Over the course of his career, he has had "[e]xtensive experience in diagnosis, treatment, follow up, second opinions[,] and care of thousands of celiac disease patients." Id. He has also served on various associations and organizations dealing with celiac disease. Id.

2. Opinion[24]

a. Althen Prong One

Dr. Lerner opined that celiac disease is polygenic[25] and that the dominant environmental factor causally associated with its development is gluten. Pet. Ex. 88 at 14. Gluten "is the offending inducer[]" of the illness and adherence to a gluten-free diet "is the only effective therapy." Id. Although Dr. Lerner acknowledged the role of gluten in causing celiac disease, here he opined that "the new appearance of [celiac disease] was caused by the Gardasil vaccination, in a cause and effect relationship." Id. at 24. He suggested three mechanisms: (1)

[22] The record contains expert reports, medical literature, office consult notes, and other evidence from Dr. Svetlana Blishteyn, M.D. relating to diagnosis and causation of POTS. See Pet. Exs. 28-39, 44-46, 78, 81-82. After those filings, Petitioner narrowed her allegations, and she now seeks compensation for celiac disease. Joint Submission at 1. Expert reports, medical literature, and other evidence not offered on the diagnosis or causation of celiac disease have been reviewed but are not summarized or discussed herein.

[23] Dr. Lerner submitted two expert reports. Pet. Exs. 88, 150.

[24] Dr. Lerner began his report by a providing a summary of Petitioner's clinical course. Since a summary of Petitioner's medical records is included in this Decision, the undersigned will not repeat Dr. Lerner's summary.

[25] Polygenic is "pertaining to or determined by the action of multiple different genes." Polygenic, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition? id=40126 (last visited Feb. 23, 2023).

the adjuvant aluminum ("alum") hydroxyphosphate; (2) an emulsifier, Polysorbate 80; and (3) a yeast, *Saccharomyces cerevisiae* ("*S. cerevisiae*"),[26] used to produce the vaccine. Id. at 23.

According to Dr. Lerner, alum is a "well-defined adjuvant . . . that is able to trigger [an] immune response." Pet. Ex. 88 at 23. He viewed alum as "a major environmental factor[] involved in autoimmunogenesis[] [] in intestinal inflammation and Crohn's disease induction." Id. In support of this opinion, Dr. Lerner cited two articles, which he authored, to explain his hypothesis of how alum could be "a potential factor" contributing to the induction of or ongoing inflammation in Crohn's disease. Pet. Ex. 139 at 1;[27] Pet. Ex. 140 at 1.[28] In both articles, Dr. Lerner explained that Crohn's disease is "a chronic relapsing intestinal inflammation in genetically susceptible individuals and is influenced by yet unidentified environmental factors." Pet. Ex. 139 at 1; see also Pet. Ex. 140 at 1.

Alum is a metal widely distributed in the environment and commonly used and primarily ingested through food, especially food grown in soil rich in the metal. Pet. Ex. 139 at 3. It is also present in food additives, coffee, cola drinks, spices, tobacco, and cannabis. Id. Regarding its immune effects, Dr. Lerner suggested that alum compounds "activate antigen-presenting cells," enhancing the "uptake of antigens and increase[ing] interleukin (IL)-1 production."[29] Id. at 5. The second article referenced by Dr. Lerner also discussed the role of "inflammasome"[30] in the pathophysiology of Crohn's disease. Pet. Ex. 140 at 4-5. Neither article discussed celiac disease.

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[26] *S. cerevisiae* is "brewers' yeast or bakers' yeast . . . used for alcoholic fermentation and in leavening bread; it is ubiquitous in the environment and although not considered a human pathogen, it is increasingly identified in fungal infections, usually in immunocompromised individuals." Saccharomyces Cerevisiae, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=104667 (last visited Feb. 23, 2023).

[27] Aaron Lerner, Aluminum Is a Potential Environmental Factor for Crohn's Disease Induction, 1107 Annals N.Y. Acad. Scis. 329 (2007). The complete article was not filed.

[28] A. Lerner, Aluminum As an Adjuvant in Crohn's Disease Induction, 21 Lupus 231 (2012). The complete article was not filed.

[29] Dr. Lerner also stated that injection of alum adjuvants can cause tissue necrosis. Pet. Ex. 139 at 5. However, there is no evidence of tissue necrosis at the site of Petitioner's HPV vaccinations. The article also discussed effects of alum hydroxide but that form of alum is not in the HPV vaccine administered to Petitioner. Pet. Ex. 349 at 12.

[30] Inflammasome is "a complex of cryopyrin, caspase-1, and other proteins, found in phagocytic cells and related to the body's system of innate immunity. Assembly of the inflammasome leads to activation of caspase-1 and resultant cleavage and activation of interleukins IL-1β and IL18 in the inflammatory response." Inflammasome, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=25203 (last visited Feb. 23, 2023).

Dr. Lerner's second proposed mechanism is based on polysorbate 80, used "as a surfactant, stabilizer[,] and emulsifier . . . in Gardasil." Pet. Ex. 88 at 23. He asserted that "[p]olysorbate 80 has been involved in the development of severe non-immunological reactions, [h]ypersensitivity reaction[,] and . . . autoimmunity induction: colitis, liver dysfunction." Id. He referenced three articles for support.

The first is a case report from Badiu et al.[31] of a 17-year-old who development urticaria, angioedema, conjunctivitis, shortness of breath, and wheezing one hour after she received her third HPV vaccine. Pet. Ex. 141 at 1. The authors concluded that she had an allergic reaction due to polysorbate 80 in the vaccine. Id. The relevance of this article is not clear, as the Petitioner's medical records do not indicate, and the experts have not opined, that Petitioner had a hypersensitivity response to the HPV vaccine or any component in the vaccine. Additionally, the patient in the Badiu et al. case report did not develop celiac disease, or any similar condition as a result of her HPV vaccination.

Polysorbate 80 is also discussed in an article authored by Chassaing et al.[32] Pet. Ex. 142. The Chassaing et al. authors conducted a study on mice predisposed to develop changes in the "microbiota composition and inflammation" and administered emulsifiers (carboxymethylcellulose or polysorbate 80) in their drinking water for 12 weeks. Id. at 2. The authors found the mice developed "low-grade inflammation and obesity/metabolic syndrome." Id. at 1. Although the complete article was not filed, and specifically the section discussing the methodology, it appears that the emulsifiers, which were administered orally, altered the "microbiota composition" in the mice, reducing levels of healthy bacteria and altering "microbial diversity." Id. at 2-3. The authors also suggested that emulsifiers promoted colitis in the susceptible mice, and therefore, they concluded that human consumption of dietary emulsifiers could affect the microbiota and increase intestinal inflammation. Id. at 3-4. Additional studies were recommended to determine whether dietary emulsifiers, including polysorbate 80, could contribute to chronic inflammatory diseases. Id. at 4. Notably, the Chassaing et al. authors examined the effects of ingesting emulsifiers in drinking water over a period of 12 weeks, not the effect of one or two doses of 50 mcg of polysorbate 80 injected intramuscularly.

In a "Letter to Editor," Dr. Lerner and Torsten Matthias[33] suggested that food additives, including emulsifiers like polysorbate 80, could cause "increased intestinal permeability." Pet.

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[31] Iuliana Badiu et al., Hypersensitivity Reaction to Human Papillomavirus Vaccine Due to Polysorbate 80, 2012 BMJ Case Reps. 1.

[32] Benoit Chassaing et al., Dietary Emulsifiers Impact the Mouse Gut Microbiota Promoting Colitis and Metabolic Syndrome, 519 Nature 92 (2015). Again, the full article was not filed. Dr. Lerner also provided a second reference on this subject, which appears to be an unpublished letter to the Editor of Nature, authored by Lerner and Torsten Matthias, commenting on the article by Chassaing et al. See Pet. Ex. 143. The focus of the letter appears to be food additives and their effect on intestinal integrity. See id.

[33] Aaron Lerner & Torsten Matthias, Multiple Food Additives Enhance Human Chronic Diseases, 4 SOJ Microbiology & Infectious Disease 1 (2016).

Ex. 144 at 1. They recommended further studies to determine whether emulsifiers play a role in disrupting "intestinal protective mechanisms." Id. Again, the context was oral ingestion, specifically the effect of processed foods containing emulsifiers, salt, and other additives. Id.

The third mechanism proposed by Dr. Lerner was based on the yeast, *S. cerevisiae*, used to produce the virus-like particles of the HPV vaccine. Pet. Ex. 88 at 23. Dr. Lerner suggested that the yeast may play a role "since celiac patients mount anti[-*S.*] *cerevisiae* antibodies (ASCA) significantly higher than controls, and the titers are gluten dependent."[34] Id. at 14. He contended that ASCA have been described in some autoimmune conditions, including celiac disease. Id.

Dr. Lerner also stated that the virus-like particles contain histones,[35] that potentially impact "DNA stability, structural integrity[,] and epigenetics." Pet. Ex. 88 at 23; Pet. Ex. 150 at 9.[36] He did not explain what histones are, how they impact DNA stability, or how this could cause the HPV vaccine to induce celiac disease.

In support of this theory, Dr. Lerner cited two references about *S. cerevisiae.* The first is only an abstract of an article by Toumi et al.,[37] which reported on a study that examined the frequency with which ASCA were found in 238 celiac patients as compared with 80 healthy controls. Pet. Ex. 145 at 1. The authors noted that ASCA were more prevalent in celiac patients who were not treated as compared to the control group (27.2% vs. 3.7%) and in adults as compared to children (35.4% vs. 21.1%). Id. In patients who adhered to a gluten-free diet as compared to healthy controls, there was no statistical difference in the results. Id. The abstract

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[34] Dr. Lerner cited an article by Viitasalo et al., reporting the findings of a study showing that celiac patients may have positive seroreactivity against ASCA and that the titers may decrease with a gluten-free diet. Pet. Ex. 92 at 1 (Lilsa Viitasalo et al., Early Microbial Markers of Celiac Disease, 48 J. Clinical Gastroenterology 620 (2014)). The authors did not reach any conclusions about the significance of their findings.

[35] Histones are "any of various simple proteins containing many basic groups, soluble in water and insoluble in dilute ammonia; the globin of hemoglobin is a histone. Combined with nucleic acids they form nucleohistone and are associated with DNA in chromatin. Some are poisonous and contain a great deal of phosphorus. Blood treated with histone is altered and has lower coagulability." Histone, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=22791 (last visited Feb. 23, 2023).

[36] An article filed by Dr. Lerner discussed the issue of low structural stability in virus-like particles that are produced in *S. cerevisiae*, but the concern was about "reduced antigenicity and immunogenicity" and not induction of any autoimmune illness. Pet. Ex. 93 (Hyoung Jin Kim et al., The Concentration of Carbon Source in the Medium Affects the Quality of Virus-Like Particles of Human Papillomavirus Type 16 Produced in *Saccharomyces Cerevisiae*, 9 Plos One e94467 (2014)).

[37] D. Toumi et al., Anti-Saccharomyces Cerevisiae Antibodies in Coeliac Disease, 32 Scandinavian J. Gasteroenterology 821 (2007).

does not mention the HPV vaccine or suggest that *S. cerevisiae* plays a role in the etiology of celiac disease.

The second article, by Kim et al.,[38] is highly technical, and Dr. Lerner did not explain it, or its relevance to his theory. See Pet. Ex. 146. The article described histones found in pseudoviruses (synthetic viruses) used to provide systems "for evaluating anti-viral agents and vaccine candidates." Id. at 1. Synthetic viruses are similar in their "structures and characteristics" to native viruses but fundamentally differ because they lack the ability to replicate. Id. Native HPV is technically difficult to produce. Id. at 2. Based on their research, the authors concluded that "the involvement of large amounts of cellular histones during [pseudovirus] formation interferes with the structural integrity of the [pseudoviruses] and affects their immunogenicity." Id. at 1. They also determined the amount of histones "most suitable" for use in an HPV pseudovirus." Id. The authors did not discuss adverse effects of the HPV vaccine, or celiac disease, or state that histones in the HPV vaccine cause any adverse effects, or otherwise relate to the issues here.

As an aside, Dr. Lerner stated that "even the intraepithelial lymphocytes that invade the HPV neoplastic lesions are gut derived, thus strengthening the gut-reproductive system cross-talks in the gut-vi[r]ginal axis." Pet. Ex. 88 at 23. Dr. Lerner did not explain this sentence or how it related to this theory. He cited to an abstract of an article authored by Kojima et al.,[39] which described a study that classified the type of lymphocytes found in cervical intraepithelial neoplastic lesions (presumably caused by HPV wild infection).[40] Pet. Ex. 147 at 1. The relevance of the abstract is not clear.

In addition to proposing the three mechanisms described above, Dr. Lerner opined that the HPV vaccine is associated with an increased incidence of autoimmune illnesses, including Bechet's syndrome, Raynaud's disease, diabetes, Hashimoto's thyroiditis, central nervous system conditions, alopecia, vasculitis, and systemic lupus erythematosus. Pet. Ex. 88 at 22; see also Pet. Ex. 150 at 6-7 (citing Pet. Exs. 190-91, 193-94). He also asserted that ulcerative colitis and Crohn's disease are new-onset illnesses that occur after HPV vaccination. Pet. Ex. 88 at 22; Pet. Ex. 150 at 7. The references cited by Dr. Lerner in support of these statements, however, do

[38] Hyoung Jin Kim et al., Characterization of Human Papillomavirus Type 16 Pseudovirus Containing Histones, 16 BMC Biotechnology 1 (2016). Only the first five pages of this 10-page article were filed.

[39] S. Kojima et al., Characterization of Gut-Derived Intraepithelial Lymphocyte (IEL) Residing in Human Papillomavirus (HPV)-Infected Intraepithelial Neoplastic Lesions, 66 Am. J. Reproductive Immunology 435 (2011).

[40] The Gardasil vaccine is prescribed for the prevention of "[c]ervical intraepithelial neoplasia." Pet. Ex. 349 at 1-2.

not mention celiac disease associated with HPV vaccination. See Pet. Ex. 133;[41] Pet. Ex. 134 at 1.[42] The second reference identified celiac disease as a "new-onset" autoimmune illness. Pet. Ex. 134 at 1.

Next, Dr. Lerner cited several articles that reported the incidence of adverse events following HPV vaccination, and he asserted they showed that celiac disease was associated with the HPV vaccination.[43] Pet. Ex. 88 at 22. One of these is authored by Cameron et al.[44] and reported on a Scottish study using hospital chart data from 2004 to 2014. Pet. Ex. 136 at 1. "[W]hile small increases in incidence were observed for Bell's palsy, [celiac] disease, ovarian dysfunction, . . . diabetes, demyelinating disease[,] and juvenile rheumatoid arthritis, none [were] statistically significant." Id. The authors acknowledged that hospital data "only capture[s] severe cases, which may under-estimate the incidence of diseases that can present with variable severity." Id. at 5. Dr. Lerner agreed and opined that many studies "were done on medical records, on hospitalized or outpatient clinics, and since [celiac disease] is mildly or hypo symptomatic clinically," patients seldom require hospitalization. Pet. Ex. 150 at 9. Thus, he believed the incidence of the disease after vaccination as reflected in these studies is underestimated. Id. at 8-9.

Dr. Lerner also referenced a Brazilian paper by Nicol et al.,[45] which reviewed peer-reviewed literature about reported adverse effects following HPV vaccinations. Pet. Ex. 137 at 1. The most common adverse effects were "pain and swelling at the injection site followed by fatigue, fever, gastrointestinal symptoms[,] and headaches." Id. at 2.

Lastly, Dr. Lerner opined that there is a "major conflict of interest" problem[46] with many HPV vaccine safety studies performed by vaccine manufactures, which he believed affects the "validity of the results and conclusions." Pet. Ex. 150 at 8. He cited the "classic example:"

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[41] David A. Geier & Mark R. Geier, A Case-Control Study of Quadrivalent Human Papillomavirus Vaccine-Associated Autoimmune Adverse Events, 34 Clinical Rheumatology 1225 (2015).

[42] Matti Lehtinen et al., Safety of the Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine in Adolescents Aged 12-15 Years: Interim Analysis of a Large Community-Randomized Controlled Trial, 12 Hum. Vaccines & Immunotherapies 3177 (2016). This is only an abstract. The full article was filed by Respondent. See Resp. Ex. T, Tab 13.

[43] One of the references was an abstract. See Pet. Ex. 134.

[44] R. L. Cameron et al., Adverse Event Monitoring of the Human Papillomavirus Vaccines in Scotland, 46 Internal Med. J. 452 (2016).

[45] A.F. Nicol et al., HPV Vaccines: A Controversial Issue?, 49 Brazilian J. Med. & Biological Rsch. 1 (2016).

[46] See Pet. Ex. 137 at 1 (recommending "a more independent monitoring system" to assess for adverse effects in order to address the conflict of issue concerns raised by Dr. Lerner).

Chao et al.[47] Id. (citing Pet. Ex. 199). Chao et al., a study supported by vaccine manufacturers like Merck, reviewed the medical records of two Kaiser facilities from 2006 and 2010 to assess the safety of the HPV4 vaccine, particularly regarding autoimmune illnesses. Pet. Ex. 199 at 1-2. Chao et al. reported that there was "no cluster of disease onset in relation to vaccination timing, dose sequence[,] or age . . . for any autoimmune condition."[48] Id. at 1.

b. Althen Prong Two

Regarding a logical sequence of cause and effect, Dr. Lerner opined that Petitioner's celiac disease is "directly connected" to the HPV vaccine. Pet. Ex. 150 at 9. He opined that the Petitioner had "definitive" celiac disease, and had "no manifestations" of the illness prior to August 30, 2011, when she received her first HPV vaccination. Id.

Dr. Lerner noted that Petitioner's family members have autoimmune illnesses, and that Petitioner had "the predisposing genetics" for celiac disease, primarily HLA-DQ2/8,[49] which is "positive in 95%" of patients with celiac disease. Pet. Ex. 88 at 21-22.

Further, Dr. Lerner explained that "[celiac disease] can present acutely and multiple acute presentations are described in the literature." Pet. Ex. 150 at 9. Celiac disease can also present with "acute, severe anemia." Id. In celiac disease, iron deficiency anemia is caused by "malabsorption due to intestinal atrophic damage, [b]lood loss[] in the stool, inadequate iron intake[,] and the anemia of chronic disease with enterocyte sequestration of iron." Pet. Ex. 88 at 17. Dr. Lerner opined that Petitioner had iron deficiency anemia commonly seen in celiac disease. Id. at 16-17.

c. Althen Prong Three

Dr. Lerner did not provide an opinion about what the expected temporal relationship would be between vaccination and disease onset for his three proposed mechanisms. For example, he did not state how long it would take for the adjuvant alum to trigger an immune response that would manifest as celiac disease.

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[47] C. Chao et al., Surveillance of Autoimmune Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine, 271 J. Internal Med. 193 (2012).

[48] For references critical of Chao et al., see Pet. Ex. 179 (L. Tomljenovic & C. A. Shaw, No Autoimmune Safety Signal After Vaccination with Quadrivalent HPV Vaccine Gardasil?, 272 J. Internal Med. 514 (2012)); Pet. Ex. 180 (L. Tomljenovic & C. A. Shaw, Human Papillomavirus (HPV) Vaccine Policy and Evidence-Based Medicine: Are They at Odds?, 45 Annals Med. 182 (2013)); Pet. Ex. 190 (Y. Shoenfeld, HPV Vaccines and Autoimmune Diseases, 272 J. Internal Med. 98 (2012)).

[49] The results of testing for these genes were not included in Petitioner's medical records, and it is not clear that Petitioner was ever tested for them. It appears that Dr. Lerner is suggesting that that Petitioner may have these genes by virtue of her diagnosis and family history, which is positive for autoimmune illnesses.

He did opine as to onset of Petitioner's celiac disease. According to Dr. Lerner, Petitioner's complaints began in the "weeks to months" after her first HPV vaccine and her "full clinical presentation," based on Dr. Kunde's records, was "apparent during Nov[ember] 2011." Pet. Ex. 150 at 9. More specifically, Dr. Lerner opined that Petitioner's onset was approximately November 10, 2011. Pet. Ex. 88 at 17. He based this opinion on the following medical record and affidavit evidence.

Petitioner first saw Dr. Kunde on January 10, 2012 and reported that her "tiredness" began in the summer of 2011. Pet. Ex. 88 at 17. In the prior two months, she had weight loss, abdominal pain, anemia, and aching bones. Id. "Extrapolating and approximating those data," Dr. Lerner opined that Petitioner's celiac disease "started to manifest around [November 10,] 2011, in between the [two] HPV vaccinations." Id. Dr. Lerner also noted that on January 11, 2012, Petitioner reported loose stools and shortness of breath that had worsened over the last week. Id.

Additionally, Dr. Lerner explained that the multiple affidavits from Petitioner, her family, and her coaches described Petitioner as extremely active and healthy prior to August 30, 2011, and that her first symptoms of illness began "weeks [to a] few months" after her first HPV vaccination. Pet. Ex. 88 at 17.

There is considerable evidence in the record about Petitioner's cross-country times and physical performance during sports both before and after vaccination. Dr. Lerner devoted several pages of his first expert report discussing his opinions about this information. See Pet. Ex. 88 at 18-21. He explained that there are "complicated, multi-fact[ed,] and interrelated aspects that influence physical performance, in general and in [celiac disease]." Id. at 18. These factors include pre-exercise nutrition, course parameters and conditions, the environment and weather, hormones and menstruation, psychological factors, and anemia. Id. at 18-19. Since information about all these factors is not available, Dr. Lerner did not believe that it was appropriate to compare Petitioner's race results before and after vaccination in order to draw conclusions as to onset of her celiac disease. Id. at 19-21.

Further, Dr. Lerner did not believe that Respondent's expert could conclude that Petitioner had anemia prior to her vaccination on August 30, 2011. Pet. Ex. 150 at 5. The initial labs that established Petitioner was anemic were not done until January 5, 2012. Id. Dr. Lerner also opined that "iron deficiency anemia can present acutely." Id. If Petitioner had anemia earlier than August 30, 2011, Dr. Lerner argued that she would have had "more severe symptomatology, clinical signs[,] and morbidity." Id. He cited an abstract of an article by Saukkonen et al.,[50] which stated that "[c]eliac patients with anemia had more severe disease than nonanemic patients in terms of the serology and a lower BMI." Pet. Ex. 104 at 1. While the abstract reported that 23% of patients (out of 163 adults) in the study had anemia when diagnosed, and this group had more gastrointestinal symptoms, higher antibody values, and

[50] J. Saukkohen et al., Clinical Characteristics and the Dietary Response in Celiac Disease Patients Presenting With or Without Anemia, 51 J. Clinical Gastroenterology 412 (2017).

lower iron values, the abstract did not speak to the question of how long it took for patients to develop the symptoms described, or whether their presentations were acute or chronic.[51] See id.

In summary, Dr. Lerner opined that Petitioner's manifestation of celiac disease was weeks to a few months after her first HPV vaccination, and specifically that her approximate onset was November 10, 2011. Pet. Ex. 88 at 17.

B. Petitioner's Expert, Dr. Yehuda Shoenfeld[52]

1. Background and Qualifications

Dr. Shoenfeld's "clinical scientific works focus on autoimmune/rheumatic diseases." Pet. Ex. 320 at 1. After graduating from medical school, he completed fellowships in hematology and oncology and a master in internal medicine from Tel-Aviv University. Pet. Ex. 205 at 3. He founded and served as Director of the Center for Autoimmune Diseases at the Sheba Medical Center in Israel. Id.; Pet. Ex. 320 at 1. He has published more than 2,000 peer reviewed papers, 28 books, and 300 chapters in medical books on vaccinations and autoimmunity. Pet. Ex. 320 at 1-2.

2. Opinion

a. Althen Prong One

Dr. Shoenfeld explained that one's response to vaccination, intended to provide protective immunity, is like a response to infection. Pet. Ex. 320 at 9. Dr. Shoenfeld opined that vaccinations, like infections, can induce autoimmunity. Id. There are several mechanisms by which infections can cause autoimmunity, and the most common of these is "molecular mimicry between infectious antigens and self-antigens."[53] Id. (emphasis omitted). Moving to vaccines, and specifically, the HPV vaccine, Dr. Shoenfeld opined that "it is [] possible that molecular mimicry plays a role in mediating autoimmunity following HPV vaccination." Id. at 11.

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[51] In another abstract filed by Dr. Lerner, the authors compared celiac patients who presented with anemia compared to those who had diarrhea on presentation. Pet. Ex. 110 at 1 (H. Abu Daya et al., Celiac Disease Patients Presenting with Anemia Have More Severe Disease Than Those Presenting with Diarrhea, 11 J. Clinical Gastroenterology & Hepatology 1472 (2013)). They found "[a]nemic patients were more than [two]-fold more likely to have severe villous atrophy and a low bone mass density at the time" of diagnosis. Id.

[52] Dr. Shoenfeld filed several expert reports. Pet. Exs. 320-21, 325, 337. Some of these expert reports discuss myasthenia gravis, POTS, CFS, and small fiber neuropathy. Petitioner is no longer seeking compensation for these alleged vaccine-related illnesses. See Joint Submission at 1. Since Petitioner now alleges that her vaccine injury is celiac disease, the portions of Dr. Shoenfeld's reports that examine other illnesses are not discussed by the undersigned.

[53] The other mechanisms Dr. Shoenfeld listed are epitope spreading, polyclonal activation of B lymphocytes, and bystander activation. Pet. Ex. 320 at 9.

Relative to molecular mimicry and the HPV vaccine, Dr. Shoenfeld suggested several avenues for cross-reactivity. The first one is taken from an article by Kanduc,[54] who investigated amino acid sequence similarity between HPV16 and human proteins to quantify the possible cross-reactivity risk of an HPV16 vaccine.[55] Pet. Ex. 344 at 1. Kanduc identified amino acid sequences[56] which "might lead to pathologies including spinal muscular atrophy, proximal muscle weakness . . . , cardiovascular and musculoskeletal abnormalities, disorders of lipoprotein metabolism . . . , and increased [susceptibility] to coronary artery disease." Id. at 2, 2-10 tbl.1. Kanduc, however, did not identify celiac disease as one of the illnesses that might be caused by cross-reactivity due to HPV16.

Next, Dr. Shoenfeld suggested that the HPV16 L1 protein antigen[57] in the vaccine shares a pentapeptide (KPPIG)[58] with the human protein "Signal Transducer and Activator of Transcription 3 ([] STAT3)." Pet. Ex. 321 at 3. He described STAT3 as a "protein that mediates cellular responses to interleukins,[59] binds to interleukin-6 (IL-6)-responsive elements identified in the promoters of various acute-phase protein genes, [] [and] [a]cts as a regulator of

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[54] Darja Kanduc, Quantifying the Possible Cross-Reactivity Risk of an HPV16 Vaccine, 8 J. Experimental Therapeutics & Oncology 65 (2009).

[55] The Petitioner received the Gardasil HPV vaccine which includes the HPV16 viral strain. See Pet. Ex. 349.

[56] The word "sequence" is used here to simplify the discussion. Kanduc's searches involved heptamer amino acid sequences, or sequences consisting of seven. Pet. Ex. 344 at 1.

[57] The Gardasil vaccine "is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant [*S.*] *cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates." Pet. Ex. 349 at 12.

[58] As support for this opinion, Dr. Shoenfeld stated that the KPPIG protein structure "is part of four epitopes that have been cataloged as immunopositive in humans at the Immune Epitope Database." Pet. Ex. 321 at 4, 5 tbl.1. It does not appear evidence from this database has been filed.

[59] An interleukin is "a generic term for a group of multifunctional cytokines that are produced by a variety of lymphoid and nonlymphoid cells and have effects at least partly within the lymphopoietic system; originally believed to be produced chiefly by and to act chiefly upon leukocytes." Interleukin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=25582 (last visited Feb. 23, 2023).

inflammatory response by regulating differentiation of naïve CD4+ T-cells[60] into T-helper Th17 or regulatory T-cells (Treg)." Id.

Relative to Dr. Lerner's opinion that *S. cerevisiae* may be associated with autoimmunity, Dr. Shoenfeld opined that the "pentapeptide KPPIG is [] present in two proteins of [*S.*] *cerevisiae*," and he suggested this may be "a possible contribution" to autoimmunity. Pet. Ex. 321 at 4 (emphasis added). Dr. Shoenfeld explained that "the autoimmunity against STAT3 triggered by HPV16 L1 might be potentiated by autoimmunity triggered by [*S.*] *cerevisiae*." Id. (emphasis added). Additionally, "[a]lterations of STAT3 are associated with childhood onset of a spectrum of autoimmune manifestations . . . including autoimmune enteropathy[61] or celiac disease." Id.

In support of his opinion that STAT3 plays a role in the development of autoimmune disease, Dr. Shoenfeld cited three articles that establish that autoimmune illnesses are found in patients with STAT3 mutations; however, they did not report that vaccinations in general, or the HPV vaccine specifically, play any role in inducing illness in those who have these mutations. Flanagan et al.[62] reported STAT3 de novo mutations[63] in five children with polyautoimmune diseases (diabetes, enteropathy, interstitial lung disease, juvenile-onset arthritis, hypothyroidism, short stature, and eczema). Pet. Ex. 345 at 1-3. Four of the five children had diabetes, short stature, and eczema. Id. at 3. The authors noted that "[t]he young age at diagnosis [0-43 weeks of age] . . . [was] consistent with STAT3 mutations causing accelerated autoimmune disease." Id. (emphasis omitted). Celiac disease was not identified as one of the illnesses associated with STAT3 mutations. See id. at 10 fig.2.

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[60] CD4 cells are "T lymphocytes that carry the CD4 antigen; they are helper T cells." CD4 Cells, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=63999 (last visited Feb. 23, 2023). Helper cells are "differentiated T lymphocytes whose cooperation (help) is required for the production of antibody against most (T-dependent) antigens." Helper Cells, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=64157 (last visited Feb. 23, 2023).

[61] Enteropathy is "any disease of the intestines." Enteropathy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=16610 (last visited Feb. 23, 2023).

[62] Sarah E. Flanagan et al., Activating Germline Mutations in *STAT3* Cause Early-Onset Multi-Organ Autoimmune Disease, 46 Nature Genetics 812 (2014).

[63] A de novo mutation is "a change in the DNA sequence of a gene that is seen for the first time in a person and has not appeared in previous generations. A de novo mutation can explain how a person can have a genetic condition that did not occur in his or her parents." De Novo Mutation, Nat'l Cancer Inst., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/de-novo-mutation (last visited Feb. 23, 2023).

Haapaniemi et al.[64] explored the role of STAT3 mutations in primary immunodeficiency syndromes. Pet. Ex. 346 at 1. By way of background, the authors explained that STATs function as "transcription factors [that] orchestrate hematopoietic [blood] cell differentiation." Id. Mutations in "STAT3 have been linked to development of immunodysregulation polyendocrinopathy enteropathy X-linked-like syndrome," "hyperimmunoglobulin E (IgE) syndrome," and "large granular lymphocytic (LGL) leukemia." Id. at 1-2 (emphasis omitted). The paper presented an evaluation of three patients who had de novo STAT3 mutations. Id. at 2. Two of the patients had "aggressive multiorgan autoimmunity and lymphoproliferation, including pediatric LGL leukemia." Id. The third patient "developed disseminated mycobacterial disease in late adolescence." Id. There is no indication that any of the children had adverse reactions to vaccinations, and it is specifically noted that patient number three had normal reactions to her vaccinations (it is not known, however, whether this included the HPV vaccination).[65] Id.

The third article, by Milner et al.,[66] described autoimmune illnesses associated with nine different STAT3 mutations. Pet. Ex. 347 at 1. The patients "exhibited a variety of clinical features, with most having lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity (lung, gastrointestinal, hepatic, and/or endocrine dysfunction), infections, and short stature." Id. The most prominent presentation was "hemolytic anemia, neutropenia, and/or thrombocytopenia." Id. at 3. Celiac disease was not referenced, and vaccination, specifically HPV vaccination, was not described as playing any role in the induction of illnesses associated with the STAT3 mutations.

In addition to implicating molecular mimicry as a mechanism, Dr. Shoenfeld also suggested that adjuvants in vaccines may play a causative role since they "induce a more vigorous immune response to the vaccinated antigens." Pet. Ex. 320 at 9-10. "The HPV vaccine uses [alum] salt as an adjuvant . . . ." Id. at 10. Dr. Shoenfeld asserted that adjuvants, which are expected to stimulate the immune system, have been "found to induce" illness. Id. He referenced "adjuvant disease"[67] and cited an article he co-authored on ASIA, an autoimmune

[64] Emma M. Haapaniemi et al., Autoimmunity, Hypogammaglobulinemia, Lymphoproliferation, and Mycobacterial Disease in Patients with Activating Mutations in *STAT3*, 125 Blood 639 (2015).

[65] Patient two was noted to have celiac disease. Pet. Ex. 346 at 2, 3 tbl.1. The authors did not suggest or opine that vaccinations caused or contributed to the patient's celiac disease.

[66] Joshua D. Milner et al., Early-Onset Lymphoproliferation and Autoimmunity Caused by Germline *STAT3* Gain-of-Function Mutations, 125 Blood 591 (2015).

[67] Dr. Shoenfeld discussed concerns related to "macrophagic myofasciitis (MMF) lesion[s] detected in patients with myalgic encephalomyelitis/[CFS]." Pet. Ex. 321 at 5. There is no evidence, however, to suggest that Petitioner had MMF or any such lesion.

syndrome which he postulated may be caused by adjuvants. Id. (citing Pet. Ex. 254).[68] In the paper, he "suggest[ed] the possibility of accelerated autoimmunity/inflammation following vaccination" due to adjuvants. Id. at 3. The paper did not identify celiac disease as one caused by adjuvants.

Regarding the effect of adjuvants, Dr. Shoenfeld stated that "vaccines are designed to hyper-stimulate antibody production . . . which is accomplished via the immuno-stimulatory properties of adjuvants." Pet. Ex. 320 at 11. He opined that adjuvants "augment the molecular mimicry of the viral particles" of the vaccine. Id. at 12. He cited an article from Watad et al.,[69] which he was a named author, that explained that adjuvants are used "to induce a more potent response to a microbial antigen" that would "produce a higher titer of antibodies, which would eventually confer better protection."[70] Pet. Ex. 341 at 1.[71] However, the paper did not suggest that adjuvants increase the likelihood of autoimmune reactions to vaccines, or play a role in the mechanism of molecular mimicry to induce an autoimmune illness.

Again, discussing hyperstimulation of the immune system, Dr. Shoenfeld suggested that "due to the high antigenicity of the [HPV vaccine]," as compared to natural HPV infection, and the "immuno-stimulatory properties of adjuvants," the HPV vaccine "may be more likely to trigger autoimmune adverse manifestation[s]" as compared to a natural infection. Pet. Ex. 320 at 11-12. He did not explain, however, how adjuvants could trigger autoimmune illness.

Another concept discussed by Dr. Shoenfeld relates to "polyautoimmunity," or "the presence of more than one autoimmune disease[]." Pet. Ex. 320 at 7; see also Pet. Ex. 337 at 1-2. He explained that patients who are "genetically prone to develop autoimmune disease are more prone to develop a second autoimmune disease." Pet. Ex. 337 at 1. He opined that "[i]f the environmental factor claimed to induce the autoimmune disease exists and was not discontinued to affect the body, there is a great possibility that it will induce . . . a second autoimmune disease." Id. Risk factors for polyautoimmunity include family history, female

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[68] Yehuda Shoenfeld & Nancy Agmon-Levin, 'Asia'—Autoimmune/Inflammatory Syndrome Induced by Adjuvants, 26 J. Autoimmunity 4 (2011).

[69] Abdulla Watad et al., Immunologist's Little Dirty Secret Finger: A Case Report of Polyautoimmunity Following an Accidental Self-Injection of Complete Freund's Adjuvant, 22 Isr. Med. Ass'n J. 393 (2020).

[70] See also Pet. Ex. 188 (A. Watad et al., Autoimmune/Inflammatory Syndrome Induced by Adjuvants (Shoenfeld's Syndrome)—An Update, 0 Lupus 1 (2017)).

[71] The article described a case report after a scientist was accidentality injected with complete Freund's adjuvant. Pet. Ex. 341 at 1. This adjuvant is not used in the HPV vaccine but has been used to induce experimental animal models of autoimmune disease, including experimental autoimmune encephalomyelitis. Id. at 1-2. Complete Freund's adjuvant "elicits cell-mediated immunity (delayed hypersensitivity), as well as humoral antibody formation." Freund Adjuvant, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=55029 (last visited Feb. 23, 2023).

gender, the presence of certain autoantibodies (including anti-gliadin immunoglobulin G ("IgG") antibodies in celiac disease), and vitamin D deficiency. Pet. Ex. 320 at 7-9.

In the context of polyautoimmunity, Dr. Shoenfeld opined that "it is more probabl[e] than not that the vaccine resulted in a pro[-]inflammatory state that contributed [to] the development of this phenomenon in the genetically susceptible [P]etitioner with a rich genetic background."[72] Pet. Ex. 321 at 10. He did not, however, explain how the HPV vaccine could cause a pro-inflammatory state or otherwise contribute to the development of celiac disease.

b. Althen Prong Two

Dr. Shoenfeld opined that Petitioner was healthy prior to vaccination, and after her HPV vaccination, she developed celiac disease. Pet. Ex. 321 at 11. He asserted that because "[t]he symptoms began following the Gardasil vaccinations, . . . the vaccine was the most probable triggering factor." Pet. Ex. 320 at 7. Similarly, he stated "in the absence of any other confounders, the time relationship, the plausible mechanism, the logical sequence, positive antibody studies, and the previously reported cases support the notion that it is more reasonable than not that the diagnosis of . . . celiac disease occurred after Gardasil administration." Pet. Ex. 321 at 11; see also Pet. Ex. 320 at 19.

Moreover, he opined that the "autoantibodies generated in response to Gardasil vaccination caused or contributed to the development of [Petitioner's] many autoimmune diseases." Pet. Ex. 325 at 1. He contended that "anti-β adrenergic receptor autoantibodies[73] specifically can be generated in response to Gardasil and those antibodies have been implicated in the development of some of [Petitioner's] conditions." Id. In Petitioner's case, he opined that these included ANA and anti-tTG antibodies. Id. Dr. Shoenfeld failed to provide any

[72] Dr. Shoenfeld cited three articles to support this statement, but the articles were not filed. See Pet. Ex. 321 at 10 (noting references 20-22 for support).

[73] An adrenergic receptor is "a site on an effector organ innervated by postganglionic adrenergic fibers of the sympathetic nervous system, classified as either α-adrenergic or β-adrenergic according to its reaction to norepinephrine and epinephrine, as well as to certain blocking and stimulating agents." Adrenergic Receptor, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=102533 (last visited Feb. 23, 2023). β adrenergic receptors "are subdivided into two basic types: β_1, found in the myocardium and causing lipolysis and cardiac stimulation, and β_2, found in smooth and skeletal muscle and liver and causing bronchodilation, vasodilation, and increased presynaptic release of norepinephrine. A third type, β_3, is atypical; it is more sensitive to norepinephrine than to epinephrine, is relatively resistant to propranolol blockade, and may be involved in lipolysis regulation in adipose tissue." β-Adrenergic Receptors, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=102536 (last visited Feb. 23, 2023).

foundational support for his opinion that the HPV vaccine can cause or did cause Petitioner to develop positive tTG or ANA antibodies.[74]

Regarding the application of polyautoimmunity here, Dr. Shoenfeld opined that "[b]ased on [Petitioner's] genetic history, her female gender, and the presence of numerous autoimmune diseases, . . . she was predisposed to autoimmune diseases prior to the HPV vaccinations, and after the HPV vaccinations transposed her first autoimmune disease, the additional diseases followed as a result." Pet. Ex. 320 at 9. Without evidentiary support, this notion of "transposition" is without foundation and conclusory.

Additionally, Dr. Shoenfeld opined that Petitioner's active participation in sports caused "an enhanced reaction to vaccine." Pet. Ex. 320 at 16. He continued, "[t]hey are like women and those who carry a genetic marker i.e., HLA DRB1. Therefore, [Petitioner] being a young woman active in sport subjected to the vaccine which contain molecular mimicry motifs together with adjuvants, gaining a genetic preponderance—developed the autoimmune reaction." Id. at 16-17 (internal citations omitted).

In support of his opinion that Petitioner's participation in sports enhanced her reaction to the vaccine, Dr. Shoenfeld cited two articles. The first, by Pascoe et al.,[75] is a literature review of published studies that examined the effects of exercise on vaccination. Pet. Ex. 267 at 1. The authors explained that "[e]xercise has been identified as a [] factor that can boost immune function in some settings and therefore potentially serve as an adjuvant for immune responses." Id. at 2. The findings suggested a "positive association between exercise and the immune response to vaccination, particularly in populations at risk for immune dysfunction, such as older adults" who have "sub-optimal responses to vaccination" due to aging. Id. at 7-8. Data in "young adult cohorts" was limited, with "only one study showing limited evidence for greater responses in participants with higher levels of physical activity." Id. at 7. The HPV vaccine was not studied.

The second article, authored by Woods et al.,[76] presented the findings of a study addressing whether moderate cardiovascular exercise or flexibility and balance training affected antibody responses to the influenza vaccination in sedentary older adults. Pet. Ex. 268 at 1. The study showed that "10 months of cardiovascular exercise training extended the antibody response afforded by influenza vaccination." Id. at 7. The HPV vaccine and younger adults were not studied, and so it is not clear whether the results would be relevant here. Assuming the results are applicable, the presumption is that exercise enhances the antibody response to vaccination.

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[74] Dr. Shoenfeld asserted that these specific antibodies are associated with "induction of several overlapping conditions, which include POTS and CFS." Pet. Ex. 325 at 2.

[75] April R. Pascoe et al., The Effects of Exercise on Vaccination Responses: A Review of Chronic and Acute Exercise Interventions in Humans, 39 Brain Behavior & Immunity 33 (2014).

[76] Jeffrey A. Woods et al., Cardiovascular Exercise Training Extends Influenza Vaccine Seroprotection in Sedentary Older Adults: The Immune Function Intervention Trial, 57 J. Am. Geriatrics Soc'y 2183 (2009).

This is a desired outcome, not an adverse outcome. The articles did not suggest that exercise increases the risk of developing autoimmune illnesses post-vaccination.

c. Althen Prong Three

Dr. Shoenfeld opined that "[P]etitioner clearly developed celiac disease after receiving the first vaccination with HPV." Pet. Ex. 321 at 2. He stated that she "developed symptoms within weeks of receiving the Gardasil vaccination, and most notably after the second dose of the vaccination." Pet. Ex. 320 at 19. While initially opining that Petitioner developed symptoms "within weeks" of vaccination, in a subsequent expert report, Dr. Shoenfeld opined that she developed symptoms "within [two] months of Gardasil administration." Id.; Pet. Ex. 321 at 11.

According to Dr. Shoenfeld, the "nature of autoimmune disease[s] and their development follow a more gradual course." Pet. Ex. 321 at 10. He cited a study by Ozawa et al.,[77] that discussed the time frame between HPV vaccination and the onset of adverse reactions. Id. Dr. Shoenfeld stated that Ozawa et al. "noted that it is rather difficult to determine the exact time of onset [of] these symptoms." Id. "Thus, the interval from an initial injection of HPV vaccine until the first awareness of these symptoms may vary among the involved patients. Taken together, while it takes some time for the diseases to fully manifest, post[-]vaccination symptoms could start with [a] quite long latency period post[-]vaccination." Id. at 11.

C. Respondent's Expert, Dr. Chris A. Liacouras

1. Background and Qualifications

Dr. Liacouras is a board-certified pediatric gastroenterologist with approximately 30 years of clinical practice. Resp. Ex. T at 1, 3. He is a Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania and at the Children's Hospital of Philadelphia in the Division of Gastroenterology, Hepatology, and Nutrition. Id. at 3; Resp. Ex. U at 2. Dr. Liacouras has also worked as the Medical Director of the Children's Hospital of Philadelphia's Center for Gastrointestinal Endoscopy, the Chairman of Pediatric Endoscopy for the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the Chairman for Pediatric Endoscopy of the American Society of Gastrointestinal Endoscopy. Resp. Ex. T at 3; Resp. Ex. U at 2-3. Over the course of his career, he has "extensively published in the field of pediatric gastroenterology;" has "evaluated between 2000-3000 pediatric patients, who have had all types of disorders of the gastrointestinal system, every year since 1991;" and has "evaluated or consulted on more than 500 pediatric patients who have had celiac disease." Resp. Ex. T at 3; see also Resp. Ex. U at 9-21.

[77] This study was not cited by Dr. Shoenfeld in his list of references at the end of his expert report, nor was it filed. See Pet. Ex. 321 at 12-13; Pet. Ex. List, filed Oct. 21, 2021 (ECF No. 279).

2. Opinion

Dr. Liacouras cited medical literature explaining that "[c]eliac disease [] is an immune-mediated systemic disorder elicited by the ingestion of wheat gliadin[78] and related prolamins[79] in genetically susceptible individuals."[80] Resp. Ex. T, Tab 19 at 1.[81] In a person with celiac disease, tTG antibodies "damage the small intestinal mucosa, which may cause villous atrophy." Resp. Ex. T, Tab 14 at 1.[82]

According to Dr. Liacouras, the presentation of celiac disease in adolescents and adults is "more insidious" than in young children. Resp. Ex. T at 5. He opined that symptoms in adolescent athletes may be present for months or years before diagnosis, due to the varied symptoms which may be vague or atypical, such as fatigue and muscle and joint pain. Id. These symptoms may occur well before a diagnosis is made. Id. Fatigue is "caused by chronic malabsorption and intestinal inflammation (loss of nutrients), anemia (decreased hemoglobin causing decreased oxygenation), and the chronicity of symptoms." Id. Anemia is caused by iron deficiency and blood loss. Id. Blood loss from the intestine is "usually related to a more prolonged chronic anemia." Id. at 6.

Many of those who have celiac disease have no significant symptoms. Resp. Ex. T at 4. Injury to the small intestine may develop slowly, and symptoms can be variable, and thus, it may take years for patients to obtain testing and diagnosis. Id. Dr. Liacouras stated that it is suspected that up to 20% of those who have the illness do not get diagnosed. Id.

Dr. Liacouras agreed that celiac disease is associated with autoimmune illnesses, including "arthritis, psoriatic skin disorders, autoimmune thyroid diseases, inflammatory bowel disease[,] and type 1 diabetes mellitus." Resp. Ex. T at 5. Important risk factors include heredity and genetics. Id. For example, the risk is increased in a person whose first-degree relatives have

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[78] "[T]he toxic fractions in gluten are a mixture of alcohol-soluble proteins called gliadins, which are rich in glutamine and proline residues that even the healthy human intestine cannot fully digest." Resp. Ex. F at 2 (Stefano Guandalini & Asaad Assiri, Celiac Disease: A Review, 168 JAMA Pediatrics 272 (2014)).

[79] Prolamins are "globular proteins found mainly in cereals; they are soluble in 70–80 per cent alcohol but insoluble in water and absolute alcohol and contain high levels of glutamic acid and proline. Examples are gliadin (found in wheat and rye) and zein (found in corn)." Prolamin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=41164 (last visited Feb. 23, 2023).

[80] For a discussion of the genetic predispositions, see Resp. Ex. F.

[81] Riccardo Troncone & Salvatore Auricchio, Celiac Disease, in Pediatric Gastrointestinal & Liver Disease 395 (Robert Wyllie et al. eds., 5th ed. 2016).

[82] Lee A. Mancini et al., Celiac Disease and the Athlete, 10 Current Sports Med. Reps. 105 (2011).

an autoimmune illness. Id. The risk is also increased in patients with Hashimoto thyroiditis and type 1 diabetes mellitus. Id.

a. Althen Prong One

Dr. Liacouras agreed that Petitioner has celiac disease but disagreed that it was caused by her HPV vaccinations. Resp. Ex. T at 4. He provided several reasons for his opinions.

First, he explained that safety studies do not show a causal association between the HPV vaccine and celiac disease. Resp. Ex. T at 6. He referenced several studies in support of this opinion. The first is by Angelo et al.,[83] and it was a post-licensure safety review of adverse drug reaction reports referred to GlaxoSmithKline, the manufacturer of the HPV-16/18 vaccine containing the alum adjuvant AS04,[84] from the United Kingdom, Netherlands, Spain, Italy, and Japan from 2007 to 2011. Resp. Ex. T, Tab 1 at 1-2. The most common adverse reactions reported were injection site pain, fever, headache, nausea, dizziness, injection site swelling, malaise, pallor, myalgia, and fainting. Id. at 2 tbl.1. Regarding immune-mediated diseases, the most common illnesses reported were Bell's palsy (VII cranial nerve palsy) and Guillain-Barré syndrome. Id. at 4 tbl.3. After analysis, the rate of these two conditions was determined to be equal to or lower than expected background rates. Id. at 4, 5 tbl.4, 6 tbl.5.

He next cited Lehtinen et al., a study of approximately 30,000 adolescents who received the HPV-16/18 vaccine (with alum containing adjuvant AS04) or hepatitis B vaccine (control group) between 2007 and 2010. Resp. Ex. T, Tab 13 at 2. Their interim results found the most common new onset autoimmune conditions reported after vaccination included ulcerative colitis, juvenile onset arthritis, celiac disease, diabetes, and Crohn's disease. Id. at 1. However, there was no increase in these conditions observed in the HPV-16/18 vaccine recipients as compared to the hepatitis B vaccine recipients. Id. The final results revealed consistent findings. Resp. Ex. V, Tab 9.[85]

Similar findings were reported by Medina et al.,[86] who compared reports of adverse events between adolescents who received the HPV-16/18 vaccine (with alum containing adjuvant AS04) and those who received the hepatitis A vaccine (control group) between 2004

[83] Maria-Genalin Angelo et al., Post-Licensure Safety Surveillance for Human Papillomavirus-16/18-AS04-Adjuvanted Vaccine: More Than 4 Years of Experience, 23 Pharmacoepidemiology & Drug Safety 456 (2014).

[84] This is not the same adjuvant in the vaccine administered to Petitioner. See Pet. Ex. 349.

[85] Dan Bi et al., Safety of the AS04-Adjuvanted Human Papillomavirus (HPV)-16/18 Vaccine in Adolescents Aged 12-15 Years: End-of-Study Results from a Community-Randomized Study up to 6.5 Years, 16 Hum. Vaccines & Immunotherapeutics 1392 (2020).

[86] Doris M. Rivera Medina et al., Safety and Immunogenicity of the HPV-16/18 AS04-Adjuvanted Vaccine: A Randomized, Controlled Trial in Adolescent Girls, 26 J. Adolescent Health 414 (2010).

and 2005 in 12 different countries. Resp. Ex. T, Tab 15 at 1-2. "The incidence of unsolicited symptoms, new onset of chronic diseases, and medically significant conditions was similar between groups." Id. at 1. The most common new onset chronic illnesses reported were "allergic rhinitis, asthma, hypersensitivity, and chronic urticaria, reported at similar incidences in both groups." Id. at 5.

A large population-based French study by Miranda et al.[87] examined the risk of autoimmune illnesses after the HPV vaccine. Resp. Ex. V, Tab 8 at 1. A total of 842,120 girls received the HPV vaccine (including Gardasil). Id. at 1, 3. There was no increased incidence of celiac disease after vaccination. Id. at 4, 4 tbl.3.

In addition to citing the studies above that failed to show a causal relationship between the HPV vaccine and celiac disease, Dr. Liacouras observed that Petitioner's expert, Dr. Lerner, agreed that there are no supportive studies. Resp. Ex. V at 1. Dr. Liacouras noted Dr. Lerner, Petitioner's gastroenterology expert, "agreed that there are no statistically significant studies that demonstrate a causal relationship between the HPV vaccine and the development of celiac disease" when he stated the studies "found [celiac disease] incidence to be increased, but not significant statistically." Id. (quoting Pet. Ex. 150 at 8).

Next, Dr. Liacouras addressed Petitioner's experts' opinions related to ASCA. He opined that there is no causal relationship between ASCA and celiac disease. Resp. Ex. T at 7. Although Dr. Liacouras agreed that ASCA have been found in celiac patients, the autoantibodies are also present in "many other inflammatory and autoimmune diseases." Id. In patients with gastrointestinal illnesses, "ASCA appear[] to be the end result of an intestinal permeability disorder and not the cause of the disease process." Id. And when ASCA are present, they usually disappear after a gluten-free diet is instituted. Id.

Dr. Liacouras cited a paper by Kotze et al.,[88] who examined the finding of ASCA in patients with Crohn's and celiac disease. Resp. Ex. T, Tab 12 at 1. They defined Crohn's disease as "a chronic inflammatory bowel disorder of uncertain etiology [with a] clinical course [] characterized by relapsing and remitting chronic intestinal inflammation." Id. The authors explained that "the cause of ASCA positivity is [] unknown and some authors have considered antibody formation as a consequence of increased mucosal permeability." Id. They also described ASCA found in patients with celiac disease at time of diagnosis that disappear after a

[87] Sara Miranda et al., Human Papillomavirus Vaccination and Risk of Autoimmune Diseases: A Large Cohort Study of Over 2 Million Young Girls in France, 35 Vaccine 4761 (2017).

[88] Lorete Maria da Silva Kotze et al., Antibodies Anti-*Saccharomyces Cerevisiae* (ASCA) Do Not Differentiate Crohn's Disease from Celiac Disease, 47 Arquivos Gastroenterologia 242 (2010).

gluten-free diet is initiated.[89] Id. at 1-3. They concluded that ASCA may be a marker of the integrity of the intestinal mucosa. Id. at 2-3.

b. Althen Prong Two

Dr. Liacouras opined that celiac disease was the cause of Petitioner's symptoms during the time frame in question, but that her celiac disease was not caused by her HPV vaccination. Resp. Ex. T at 4, 8. He explained that Petitioner had a family history of autoimmune illnesses, and "individuals who develop celiac disease frequently manifest a family history of other autoimmune disorders." Id. at 8.

c. Althen Prong Three

Regarding onset, Dr. Liacouras opines that "more likely than not, [] [Petitioner] began to develop celiac disease before the Summer of 2011[,] and that the majority of the symptoms that [Petitioner] initially reported beginning in the Summer and Fall of 2011 were attribut[able] to her celiac disease." Resp. Ex. T at 4.

As a frame of reference, Dr. Liacouras summarized the relevant facts. In January 2012, when Petitioner was diagnosed with celiac disease, she had "severe iron deficiency anemia (decreased MCV, serum iron[,] and ferritin)." Resp. Ex. T at 7. The prior Summer (2011), approximately five or six months before her diagnosis, "[she] began to experience fatigue." Id. Petitioner reported "shortness of breath and weak legs in early September 2011."[90] Id. Dr. Liacouras explained that these symptoms (fatigue, shortness of breath, and weak legs) are "typical for chronic iron deficiency anemia and malabsorption and indicate that [Petitioner's] celiac disease began prior to these symptoms." Id. "Specifically, fatigue is a common feature of celiac disease and is almost always related to anemia." Id. Moreover, "[t]he development of iron deficiency amenia and fatigue is not an acute manifestation but instead is a chronic process." Id. He opined that Petitioner's fatigue predated her first HPV vaccination on August 30, 2011 and thus, the onset of her celiac disease occurred prior to vaccination. Id.

[89] Papp et al. reported that "[t]he presence of anti-glycan antibodies [including ASCA] in [celiac disease] seems to be secondary to the impaired small bowel mucosa which can lead to increased antigen presentation." Resp. Ex. T, Tab 17 at 1 (Maria Papp et al., Anti-Microbial Antibodies in Celiac Disease: Trick or Treat?, 15 World J. Gastroenterology 3891 (2009)). The antibodies disappear "after strict adherence to long-term [gluten-free diet]." Id. at 7.

[90] In her affidavit, Petitioner averred that at a cross-country meet on September 10, 2011, she had pain in her legs, was weak, and had difficulty breathing. Pet. Ex. 60 at ¶ 11. Petitioner's mother also averred that Petitioner had shortness of breath and weak legs on the same day, September 10, 2011. Pet. Ex. 61 at ¶ 6.

To support his opinions as to disease onset, Dr. Liacouras referenced several articles that discuss the development of symptoms associated with celiac disease. The first, by Fuchs et al.,[91] discussed "factors associated with long diagnostic delay in celiac disease" in a study of 825 adults with the illness. Resp. Ex. T, Tab 10 at 1. Of the total, "261 patients had diagnostic delay of [greater than] 10 years." Id. at 2. "Female gender, neurological or musculoskeletal disorders[,] and presence of diarrhea, abdominal pain, and malabsorption were associated with prolonged delay" in diagnosis. Id. at 1. The majority (559 or 68%) of the 825 patients had gastrointestinal symptoms before diagnosis. Id. at 3. The authors found it "surprising that one of the most characteristic and classic signs of celiac disease, malabsorption, increased the risk for long delay." Id. at 5.

Similarly, Norström et al.[92] studied 1,031 adult patients with celiac disease and found "[t]he mean delay from the first symptoms . . . to diagnosis was 9.7 years and the median delay was 4 years." Resp. Ex. T, Tab 16 at 1, 3. Cranney et al.[93] also studied the "length and nature of the diagnostic process" in 2,681 patients with celiac disease. Resp. Ex. T, Tab 5, at 1-2. Sixty-eight percent reported extreme weakness/tiredness and 66% had anemia prior to diagnosis. Id. at 4 tbl.1. "The mean delay in diagnosis after onset of symptoms was 11.7 years" with a "median delay" of five years. Id. at 4.

For patients who present with anemia, Dr. Liacouras cited Paez et al.,[94] who reported "a mean delay in the diagnosis of celiac disease of 3.5 years in patients who present with nongastrointestinal symptoms." Resp. Ex. V, Tab 3 at 2. Nongastrointestinal symptoms include fatigue and anemia. Id. Bottaro et al.[95] reported that "iron-deficiency anemia appeared to be the most frequent extraintestinal marker of [celiac disease]." Resp. Ex V, Tab 4 at 3. Dr. Liacouras also cited a case report by Dina et al.[96] that described a 38-year-old female who had a history of anemia for seven years before diagnosis. Resp. Ex. T, Tab 8 at 1. The authors noted that "[i]ron deficiency anemia is [] the most frequent laboratory manifestation of celiac disease." Id. at 3.

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[91] Valma Fuchs et al., Factors Associated with Long Diagnostic Delay in Celiac Disease, 49 Scandinavian J. Gastroenterology 1304 (2014).

[92] Fredrik Norström et al., Delay to Celiac Disease Diagnosis and Its Implications for Health-Related Quality of Life, 11 BMC Gastroenterology 1 (2011).

[93] Ann Cranney et al., The Canadian Celiac Health Survey, 52 Digestive Disease & Scis. 1087 (2007).

[94] Marco A. Paez et al., Delay in Diagnosis of Celiac Disease in Patients Without Gastrointestinal Complaints, 130 Am. J. Med. 1318 (2017).

[95] G. Bottaro et al., The Clinical Pattern of Subclinical/Silent Celiac Disease: An Analysis on 1026 Consecutive Cases, 94 Am. J. Gastroenterology 691 (1999).

[96] I. Dina et al., Long-Standing Iron-Deficiency Anemia in an Atypical Celiac Disease—A Case Report, 7 J. Med. & Life 99 (2014).

Given Petitioner's presentation characterized by fatigue and anemia, and the findings of the studies cited above, Dr. Liacouras concluded that "it is more likely tha[n] not that [Petitioner] began to develop celiac disease well before the Summer of 2011." Resp. Ex. T at 7.

Further, Dr. Liacouras opined that the symptoms that Petitioner reported "as early as September 10, 2011[] occurred much too quickly to be associated with the possibility of HPV induced celiac disease from a vaccine administered on August 30, 2011" because "[t]he symptoms of celiac disease take months or years to manifest." Resp. Ex. T at 7. Dr. Liacouras opined that Petitioner's onset occurred between September 10 to 17, 2011, when she complained of shortness of breath and weak legs. Id. at 1; Resp. Ex. V at 2. He opined that onset was too soon after vaccination to attribute the illness to the HPV vaccine because these symptoms "would not occur within a few days of first developing the intestinal abnormalities of celiac disease." Resp. Ex. V at 2. The symptoms of celiac disease relate to "iron deficiency anemia or severe chronic intestinal inflammation" and these conditions take "a significant amount of time to occur and develop after the beginning stages of celiac disease." Id.

To support his opinion, Dr. Liacouras cited a review paper by Stein et al.,[97] who reported that 32%-69% of patients with celiac disease have amenia, and approximately 80% of celiac patients with anemia have iron deficiency. Resp. Ex. V, Tab 1, at 3 tbl.1, 6. The most prominent cause of anemia is abnormal absorption of iron, along with bleeding and inflammation of the intestine. Id. at 3 tbl.1. Anemia is defined "as a hemoglobin [] level < 12 g/dL in women." Id. at 2. Iron deficiency is present when "serum ferritin levels [are] below 15-100 ng/mL . . . and transferrin saturation [] [is] below 16%-20%." Id.

"A normal hemoglobin in a teenage female is approximately 12." Resp. Ex. V at 3. Dr. Liacouras opined that it would take "at least" six to 12 months for a patient with "undiagnosed celiac disease" to develop severe anemia (hemoglobin of 8.7). Id. He cited two papers that support his opinion. The first is a treatise on iron deficiency anemia by Braunstein,[98] who described the stages of iron deficiency. Resp. Ex. V, Tab 5. "In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores." Id. at 2. "During later stages, deficiency impairs [red blood cell] synthesis, ultimately causing anemia." Id. Anemia is usually caused by blood loss and less commonly, malabsorption. Id. at 1. When anemia is discovered, "occult blood loss should be suspected until proven otherwise." Id. Symptoms of iron deficiency are "due to anemia" and include "fatigue, loss of stamina, shortness of breath, weakness, dizziness, and pallor." Id. at 3.

More specifically, each of Braunstein's five stages of iron deficiency are described below.

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[97] Jürgen Stein et al., Anemia and Iron Deficiency in Gastrointestinal and Liver Conditions, 22 World J. Gastroenterology 7908 (2016).

[98] Evan M. Braunstein, Iron Deficiency Anemia, Merck Manual, https://www.merckmanuals.com/professional/hematology-and-oncology/anemias-caused-by-deficient-erythropoiesis/iron-deficiency-anemia (last visited Dec. 16, 2019).

Stage 1 is characterized by decreased bone marrow iron stores; hemoglobin [] and serum iron remain normal, but the serum ferritin level falls to < 20 ng/ml. The compensatory increase in iron absorption causes an increase in iron-binding capacity (transferrin level).

During stage 2, erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when serum iron falls to < 50 µg/dl (< 9 µmol/L) and transferrin saturation to < 16%. The serum transferrin receptor level rises (> 8.5 mg/L).

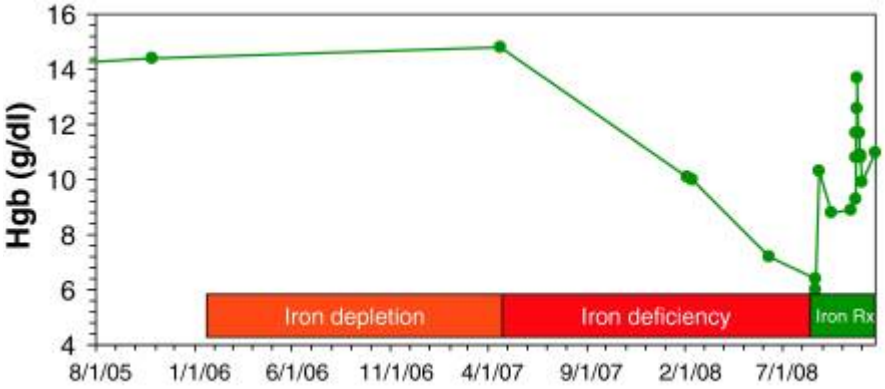
During stage 3, anemia with normal-appearing [red blood cells] and indices develops.

During stage 4, microcytosis and then hypochromia develop.

During stage 5, iron deficiency affects tissues, resulting in symptoms and signs.

Resp. Ex. V, Tab 5 at 5 (emphasis omitted).

Dr. Liacouras also cited a diagram illustrating how iron deficiency anemia effects hemoglobin over time in a patient with severe anemia.



Resp. Ex. V, Tab 6 at 4 fig.1.[99]

Lastly, Dr. Liacouras disagreed with Dr. Lerner's opinion that if Petitioner had anemia prior to August 2011, she would have presented with a "much more severe symptomatology, clinical signs[,] and morbidity." Resp. Ex. V at 3 (quoting Pet. Ex. 150 at 5). Dr. Liacouras

[99] Amy Zhu et al., Evaluation and Treatment of Iron Deficiency Anemia: A Gastroenterological Perspective, 55 Digestive Diseases & Scis. 548 (2010).

opined that a study from Repo et al.[100] found "patients with celiac disease and anemia do not necessarily have more severe clinical symptoms." Id. at 4. Repo et al. studied the incidence of anemia and iron deficiency in 102 children with "potential" celiac disease as well as those who had already developed "mucosal atrophy" and found that "anemia and iron deficiency . . . may [] be present in children with normal villous morphology." Resp. Ex. V, Tab 7 at 1-2. "The main finding . . . was that, even if more common in children with severe mucosal atrophy, celiac disease-associated anemia and iron deficiency are a continuum and may appear even before morphological villous damage." Id. at 5. Although anemia was seen in almost two-thirds (63%) of children with total villous atrophy, it was also present in one-fifth (22%) of children with partial or subtotal villous atrophy. Id. at 1.

Further, Dr. Liacouras observed that Petitioner "had no visible gastrointestinal bleeding; instead, she had [three] positive hemoccult tests which suggest a chronic slow loss of blood and iron, not an acute, rapid [gastrointestinal] blood and iron loss." Resp. Ex. V at 3. In conclusion, Dr. Liacouras opined that like other celiac patients, it is "very likely" that Petitioner's celiac disease caused her symptoms in the Summer of 2011, and her symptoms "very likely" began many months before that, but that her diagnosis was delayed until January 2012. Id. at 4-5.

D. Respondent's Expert, Dr. Eric Lancaster[101]

1. Background and Qualifications

Dr. Lancaster obtained his M.D. and Ph.D. from the University of Maryland before completing an internship, neurology residency, and neuromuscular fellowship at the University of Pennsylvania. Resp. Ex. A, Tab 1 at 1. Dr. Lancaster is board certified in neurology, electromyography, and neuromuscular medicine. Id. at 2. He has worked as an Assistant Professor of Neurology at the University of Pennsylvania since 2013. Id. at 1. Dr. Lancaster has authored or co-authored over 20 peer-reviewed publications. Id. at 3-4. His clinic is "focused on autoimmune neurological diseases." Resp. Ex. A at 1.

2. Opinion

Dr. Lancaster did not offer opinions related to the appropriateness of Petitioner's diagnosis of celiac disease and deferred to Dr. Liacouras on that subject. Resp. Ex. W at 3. The

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[100] Marleena Repo et al., Amenia and Iron Deficiency in Children with Potential Celiac Disease, 64 J. Pediatric Gastroenterology & Nutrition 56 (2017).

[101] Dr. Lancaster filed five expert reports. Resp. Exs. A-C, E, W. The first three reports addressed opinions of Dr. Blitshyten, Petitioner's initial expert. Petitioner no longer offers Dr. Blitshyten as an expert, and therefore, the earlier reports by Dr. Lancaster addressing her opinions are not discussed herein. Only Dr. Lancaster's expert report identified as Respondent's Exhibit W is discussed here. Further, to the extent that this expert report covers subject matter outside the scope of the issues identified in the Joint Submission, that subject matter is not addressed. Therefore, Dr. Lancaster's opinions about POTS, CFS, and small fiber neuropathy are not discussed.

focus of his opinions was on the immune mechanisms proposed by Petitioner's expert, Dr. Shoenfeld. Id. at 1.

Regarding molecular mimicry, Dr. Lancaster opined that Dr. Shoenfeld relied on "low-level homology between [human] proteins and a vaccine protein to argue that molecular mimicry is a plausible mechanism." Resp. Ex. W at 8. Dr. Lancaster identified a fundamental problem with this approach: that such homologies can occur by chance. Id.

Dr. Lancaster explained that to some extent, "[l]ow-level homology between large proteins will occur by pure chance." Resp. Ex. W at 8. "There are only 20 amino acids that form the basic linear structure of proteins . . . [s]o proteins with hundreds or thousands of amino acids will inevitably share short runs of identical amino acid sequences with other proteins by random chance." Id. He cited a paper by Silvanovich et al.,[102] who analyzed short amino acid sequence matches (eight or less amino acids) to determine the potential for cross-reactivity between a "protein of interest and a known allergen." Id. at 1. They reported that "simply searching matches of short peptide with known allergens adds little value to assess protein for allergenic potential" as findings could be a "product of chance." Id. at 1, 7.

Regarding Petitioner's theory based on the alum adjuvant, Dr. Lancaster cited a paper by Ameratunga et al.,[103] in which the authors concluded that "[c]urrent data do not support causation of ASIA." Resp. Ex. W, Tab 10 at 1. The authors identified a number of problems with the proposed illness, including the broad and non-specific diagnostic criteria, which include fever, autoimmunity, and chronic fatigue. Id. at 2. They also explained that "[t]he strongest argument against the existence of ASIA caused by [alum]-containing vaccine adjuvants is the decreased incidence of autoimmune diseases in patients receiving [alum]-containing allergen-specific [immunotherapy]" reported in a large study from Denmark. Id. at 3 (emphasis omitted).

VII. DISCUSSION

A. Standards for Adjudication

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

[102] Andre Silvanovich et al., The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity, 90 Toxicological Scis. 252 (2006).

[103] Rohan Ameratunga et al., Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA), 5 J. Allergy & Clinical Immunology Practice 1551 (2017).

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

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

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

B. Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378,

1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

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

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

C. Causation

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

Because Petitioner does not allege that she suffered a Table injury, she must prove that a vaccine caused her injury. To do so, she must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and her injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("Althen Prong Three"). § 13(a)(1); Althen, 418 F.3d at 1278.

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

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

D. Analysis

1. Althen Prong One: Petitioner's Medical Theory

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

than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner has failed to prove by preponderant evidence that the HPV vaccinations she received caused her celiac disease for the following reasons.

First, Petitioner's experts' opinions are not supported by foundational evidence, are not developed, and are overall conclusory. Starting with Dr. Lerner, he proposes a mechanism based on the alum adjuvant. But he never explains how alum triggers an immune response, and how that immune response causes celiac disease. Similarly, he opines that alum is involved in the "autoimmunogenesis" of intestinal inflammation and Crohn's disease, but again he does not explain the process for how that happens. The articles he cites state that the etiology of Crohn's disease is not known. The trigger of celiac disease is known to be gluten. Dr. Lerner does not recognize differences between the two diseases or explain how causal theories that may apply to Crohn's disease are relevant in the context of celiac disease.

More fundamentally, Dr. Lerner does not explain how alum plays any role in the etiology of celiac disease, a disease he acknowledges is caused by an abnormal immune response to gluten. The articles cited by Dr. Lerner about alum do not mention celiac disease. And Dr. Lerner does not identify any evidence to suggest that alum plays any role in the development of celiac disease. Therefore, there is not preponderant evidence that alum plays any role in the development of celiac disease.

The same problems apply to Dr. Lerner's theory based on polysorbate 80. Dr. Lerner does not explain how the emulsifier causes celiac disease or otherwise plays any role in its etiology. He cites a case report of a patient who had a hypersensitivity reaction to the HPV vaccine, and polysorbate 80 was suspected as the trigger of the hypersensitivity reaction. But he cites no evidence to support a conclusion that celiac disease is triggered by a hypersensitivity reaction to polysorbate 80. Moreover, the patient described in the case report did not develop celiac disease. And Petitioner has not been diagnosed with hypersensitivity to polysorbate 80.

Dr. Lerner filed several articles describing how emulsifiers added to ingested water or food could alter the microbiota of the intestine and increase intestinal inflammation. The HPV vaccine is administered intramuscularly, not orally. There was no oral ingestion of polysorbate 80 over a period of weeks or months here. Therefore, the relevance of these articles is not clear. Further, Petitioner filed no evidence to support a conclusion that polysorbate 80 plays a role in the development of celiac disease.

The third mechanism offered by Dr. Lerner is based on the yeast used to make the HPV vaccine, *S. cerevisiae*, more commonly known as baker's yeast or brewer's yeast, which is used in the production of food and wine. Dr. Lerner filed articles showing that ASCA have been described in patients with celiac disease. The authors, however, did not suggest or conclude that the yeast contributed to the etiology of celiac disease. The same is true for the idea that histones may contribute to causation. The paper by Kim et al. describes histones and discusses HPV pseudoviruses; however, the authors appear to be interested in creating pseudoviruses to better simulate real viruses for use in research and development of drugs and vaccines. The issue

related to histones did not relate to disease causation. Regardless, the authors did not discuss adverse effects of the HPV vaccine, or celiac disease, and it does not appear to be relevant to the issues in dispute here.

Moving to Dr. Shoenfeld's opinions, his theories are also unsupported by the evidence and conclusory in nature. For example, in support of his opinion based on the alum adjuvant in the vaccine, he cites an article he co-authored on autoimmune/inflammatory syndromes induced by adjuvants, or ASIA. The authors do not reach any conclusions, although they question the "possibility of accelerated autoimmunity/inflammation following vaccination." Pet. Ex. 254 at 3. Other than this weak reference, Petitioner offers no evidence that alum plays a role in molecular mimicry or that it causes or contributes to celiac disease.

The same is true of Dr. Shoenfeld's opinions about hyperstimulation. He fails to explain how the HPV vaccine, or the alum adjuvant, caused hyperstimulation, the relevance given his theory of molecular mimicry, or otherwise provide evidence that it causes celiac disease.

As for the concept of polyautoimmunity, it does not appear to be a mechanistic theory for how the HPV vaccine can cause celiac disease. That some patients may have more than one autoimmune illness, or have risk factors for autoimmune illnesses, is not in dispute.

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

Second, in addition to lacking evidentiary support and being conclusory, Petitioner's experts' opinions are not held to the requisite legal standard of preponderance (more likely than not). Regarding Dr. Lerner, at the end of his first expert report he wrote, "I declare that the new appearance of [celiac disease] was caused by the Gardasil vaccination[] in a cause and effect relationship. Several potentially mechanistic pathways[] relating the HPV vaccine to [celiac disease] induction[] are suggested." Pet. Ex. 88 at 24. The word "potentially" is an adverb "used to describe the possible results or effects of something."[104] Dr. Lerner uses the word "potentially" again in his second report, stating that viral-like proteins generated in *S. cerevisiae* "can impact DNA stability . . . thus potentially connecting HPV vaccine composition to autoimmunity." Pet. Ex. 150 at 5. He also uses the word "might" to express his opinion: "[Petitioner] might represent such a case were her genetic susceptibility, in a high risk family for

[104] Potentially, Merriam-Webster, https://www.merriam-webster.com/dictionary/potentially (last visited Feb. 23, 2023).

autoimmune condition, developed post HPV vaccination." Id. at 6. "Might" is "used to say that something is possible."[105]

In addition to the examples above, Dr. Lerner uses language that is insufficient to establish the preponderant standard. Dr. Lerner explains that he "never pretended for causal relationship between ASCA and [celiac disease]." Pet. Ex. 150 at 5. Thus, he disavows his prior statement related to the presence of antibodies (ASCA) or how they implicate a causal role played by *S. cerevisiae*. At the conclusion of his second expert report, Dr. Lerner states, "It is my personal opinion that [Petitioner's] post [HPV vaccination] [celiac disease] is directly connected to the vaccine[] in a cause and effect relationship." Id. at 9. While this statement is stronger, it is inconsistent with most of Dr. Lerner's opinions which are expressed in a more tentative manner. Overall, the language used by Dr. Lerner is insufficient to support causation.

Dr. Shoenfeld also uses the words "possible" or "might" when offering opinions.[106] For example, when describing molecular mimicry, he states, "it is also possible that molecular mimicry plays a role in mediating autoimmunity following HPV vaccination." Pet. Ex. 320 at 11. The Kanduc paper referenced by Dr. Shoenfeld related to molecular mimicry is entitled, "Quantifying the possible cross-reactivity risk of an HPV16 vaccine." Pet. Ex. 344 at 1. Similarly, Kanduc uses the word "might." She describes amino acid sequences that "might lead to pathologies." Id. at 2. Regarding the sequence KPPIG, Dr. Shoenfeld states that it is a "possible contribution." Pet. Ex. 321 at 4. In the article about adjuvants, the authors (including Dr. Shoenfeld) described the "possibility of accelerated autoimmunity/inflammation following vaccination." Pet. Ex. 254 at 3.

Opinions expressed as possibilities, however, are not sufficient to establish causation. See, e.g., Garner v. Sec'y of Health & Hum. Servs., No. 15-063V, 2017 WL 1713184, at *16 (Fed. Cl. Spec. Mstr. Mar. 24, 2017) (providing the Petitioner's expert provided conclusory reasoning for "possible" vaccine causation is "not sufficient"), mot. for rev. denied, 133 Fed. Cl. 140; LaCour v. Sec'y of Health & Hum. Servs., No. 90-316V, 1991 WL 66579, at *5 (Fed. Cl. Spec. Mstr. Apr. 15, 1991) ("Expert medical testimony which merely expresses the possibility—not the probability—of the occurrence of a compensable injury is insufficient, by itself, to substantiate the claim that such an injury occurred."); Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Waterman, 123 Fed. Cl. at

[105] Might, Merriam-Webster, https://www.merriam-webster.com/dictionary/might (last visited Feb. 23, 2023).

[106] This is not the first time Dr. Shoenfeld has been criticized for conclusory opinions. See, e.g., Garner v. Sec'y of Health & Hum. Servs., No. 15-063V, 2017 WL 1713184, at *16 (Fed. Cl. Spec. Mstr. Mar. 24, 2017) ("Conclusory reasoning on Dr. Shoenfeld's part that this is possible—rather than by offering literature or evidence—is not sufficient . . . ."), mot. for rev. denied, 133 Fed. Cl. 140; Crutchfield v. Sec'y of Health & Hum. Servs., No. 09-0039V, 2014 WL 1665227, at *11-13 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) (criticizing Dr. Shoenfeld's opinions as "poorly explained, flawed, and unpersuasive on its face" (emphasis omitted)), aff'd, 125 Fed. Cl. 251.

573-74 (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard); Boatmon, 941 F.3d at 1359-60. While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

The third reason for the undersigned's findings is based on Dr. Shoenfeld's use of medical literature. At times he appears to mischaracterize or stretch the findings of the authors to support his assertions. For example, Dr. Shoenfeld proffers the medical theory of molecular mimicry and cites Kanduc, who includes a table of protein sequences shared between HPV 16 and human proteins. See Pet. Ex. 344 at 2-10 tbl.1. Kanduc "postulate[s] that targeting these human antigens might induce many of the syndromes" described. Id. at 2. However, celiac disease is not one of the illnesses identified by Kanduc. Therefore, Kanduc does not provide evidence of a shared molecular mimic that could lead to celiac disease. Dr. Shoenfeld does not acknowledge this limitation when offering his opinion.

Next, Dr. Shoenfeld identifies a protein sequence in *S. cerevisiae* (KPPIG) as a "possible contribut[or]" to autoimmunity. Pet. Ex. 321 at 3-5. However, his discussion about this protein sequence is difficult to follow, and although Dr. Shoenfeld alleges that the HPV vaccine contains the sequence, the undersigned was unable to verify this assertion in the exhibits filed. Assuming that it does, and further assuming the sequence is also found in the STAT3 protein, Dr. Shoenfeld does not explain how the mere presence of this example of shared homology could, though molecular mimicry, induce celiac disease.

Further, the medical literature cited by Dr. Shoenfeld about STAT3 relates to de novo mutations and their role in causing disease in young children. Dr. Shoenfeld offers no explanation about how molecular mimicry could cause a de novo mutation, which are mutations present at birth. He does not explain what de novo mutations are or how they occur. And he does not distinguish diseases caused by de novo mutations from those he asserts are vaccine-related. Worse, the manner in which he describes the articles suggests that the HPV vaccine could cause the mutations.

In contrast to Petitioner's experts, the experts offered by Respondent, particularly Dr. Liacouras, provide cogent opinions and large-scale safety studies that have failed to show an increased risk in celiac disease associated with the HPV vaccination. Dr. Liacouras referenced relevant safety studies by Angelo et al., Lehtinen et al., Medina et al., Miranda et al., and Bi et al., which looked for but did not find a causal association between the HPV vaccine and celiac disease. Dr. Liacouras also persuasively explained the weaknesses of each of Petitioner's suggested causal mechanisms and he cited relevant medical literature in support of these opinions.

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

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

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

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

The undersigned finds Petitioner has failed to prove by preponderant evidence that the HPV vaccine caused her celiac disease for the following reasons.

First, the experts agree that Petitioner was correctly diagnosed with celiac disease. Both parties filed medical literature that explains the causal mechanisms that induce the illness. And these mechanisms do not implicate HPV infections or vaccines. Thus, there is no reason to implicate the HPV vaccination as a causal agent for Petitioner's celiac disease.

Respondent filed an article, co-authored by Dr. Lerner, that explains the abnormal immune responses to gluten in those with celiac disease. Pet. Ex. 101.[107] Celiac disease is caused by an inflammatory response to the ingestion of gluten in genetically susceptible individuals. Id. at 1. "The currently accepted theory [of causation of celiac disease] is that susceptible people . . . exhibit an aberrant response to dietary gluten, and that the resulting small intestinal damage is caused by locally activated $CD4^+$ T-lymphocytes" through a complex process that leads to cytokine production and causes intestinal "mucosal damage."[108] Id. at 4. According to Dr. Lerner's article, the cause of celiac disease is an immune response to gluten, not vaccination.

[107] Shimon Reif & Aaron Lerner, Tissue Transglutaminase—The Key Player in Celiac Disease: A Review, 3 Autoimmunity Revs. 40 (2004).

[108] For a thorough description of the mechanistic process described in an article co-authored by Dr. Lerner, see Resp. Ex. 101 at 4.

Further, Petitioner tested positive for a serological marker of celiac disease—tTG. In the article described above, co-authored by Dr. Lerner, the authors explain that tTG is "directly involved in the pathogenesis of the disease" by interfering with "differentiation of epithelial cells," affecting the "differentiation of intestinal epithelium," contributing to the production of "inflammatory cytokines," and "generating gluten peptides, which stimulates the T cells in the small intestine of [celiac disease] patients." Pet. Ex. 101 at 3-4. Thus, based on the medical literature filed by Petitioner, there is no need to implicate Petitioner's HPV vaccinations as a cause or contributing factor to her celiac disease.

Moreover, Petitioner's treating physicians did not suggest that her HPV vaccinations played a causal role in her celiac disease. Instead, they attributed it to gluten ingestion. Petitioner's gastroenterologist Dr. Kunde ordered lab tests confirming her tTG and ANA were abnormal, and he ordered an endoscopy, which was interpreted to be consistent with celiac disease. Dr. Kunde did not attribute Petitioner's illness to her vaccinations.

Petitioner improved when she avoided ingestion of gluten. In October and December 2012, Petitioner followed a gluten-free diet and her tTG decreased to normal or near normal, and her symptoms only occurred when she ingested gluten. See Pet. Ex. 65 at 102-03, 123. When Petitioner avoided the cause of her illness, she improved, confirming that gluten was the triggering agent, not vaccination.

Regarding Petitioner's theories based on alum, polysorbate 80, or *S. cerevisiae*, there is no indication in the medical records that her treating doctors ever considered these as causes of her celiac disease, or that she was tested for any abnormalities related to these three alleged factors. The same is true for the theory based on alteration or mutation of STAT3. And there is no evidence that Petitioner had genetic testing which showed she had this mutation.

For the reasons described above, the undersigned finds that Petitioner has failed to provide preponderant evidence of a logical sequence of cause and effect required under Althen Prong Two.

3. Althen Prong Three: Proximate Temporal Relationship

Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. Petitioner must provide "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that

[P]etitioner must posit a medical theory causally connecting the vaccine and injury"), aff'd, 475 F. App'x 765 (Fed. Cir. 2012).

Both of Petitioner's experts opine that Petitioner was asymptomatic and healthy prior to her first HPV vaccination administered August 30, 2011. And both opine that Petitioner began having celiac disease related complaints in the "weeks to months" after her first vaccination. Specifically, Dr. Lerner places onset on approximately November 10, 2011, while Dr. Shoenfeld never opined as to a specific date of onset, but offered a range of "within [two] months" after vaccination. Pet. Ex. 88 at 17; Pet. Ex. 320 at 19; Pet. Ex. 321 at 11. In contrast, Respondent's gastroenterologist Dr. Liacouras opined that Petitioner's onset was prior to her first vaccination (August 30, 2011), and that iron deficiency anemia, which Petitioner had, takes time to develop, and so he concludes that Petitioner's illness began prior her vaccination. Resp. Ex. T at 4, 7; Resp. Ex. V at 2-5. Dr. Liacouras also opines that Petitioner's symptoms attributable to her celiac disease began too soon after her first HPV vaccination to attribute the illness to vaccination. Resp. Ex. T at 4, 7; Resp. Ex. V at 2-3.

The medical records establish that in 2010, Petitioner was healthy and participating in sports without difficulty.[109] On August 30, 2011, she complained of bilateral hip pain while running. She received her first HPV vaccination that day. Petitioner and her mother both averred that at a cross-country meet on September 10, 2011, Petitioner had pain and/or weakness in her legs and shortness of breath. On January 5, 2012, Petitioner saw her primary care provider, Dr. Dekeyser, complaining of shortness of breath during exertion "for a couple months," diarrhea, and severe abdominal pain. Pet. Ex. 14 at 3. At this visit, labs revealed Petitioner was severely anemic, her hemoglobin was 8.7 (normal range 12.0-14.5 gm/dL), and her iron level was very low at 9 (normal 40-150 mcg/dl). She also had occult blood in the stool. After referral to a gastroenterologist, and further studies, she was diagnosed with celiac disease, and her abnormal lab results were attributed to her illness.

The signs and symptoms which Petitioner's specialists attributed to her celiac disease included shortness of breath, fatigue, iron deficiency, and anemia. These signs and symptoms, however, were not present at the time of her first HPV vaccination on August 30, 2011. Therefore, the undersigned finds that prior to and on August 30, 2011 (date of her first HPV vaccination), Petitioner was asymptomatic.

However, Respondent's expert's, Dr. Liacouras' opinions and explanation of celiac disease suggests that there are two questions inherent to understanding onset in the context of celiac disease. Although the symptoms (shortness of breath, fatigue, and anemia) may herald the disease, the pathological process that causes these symptoms begins earlier. Thus, the two

[109] The undersigned has reviewed all the evidence regarding Petitioner's track meets and cross-country race times and is unable to reach any conclusions or render any findings with respect to this evidence. Dr. Lerner raised legitimate concerns about the value of this evidence due to the complicated and multifactorial aspects including environment, weather, and course conditions. The undersigned finds Dr. Lerner's opinions about using this information to be persuasive, and therefore, does not factor it into her findings as to onset.

questions are (1) when did Petitioner experience the initial symptoms of celiac disease, and (2) when was the disease pathology onset that led to these symptoms.

Dr. Liacouras effectively referenced medical literature explaining that there is often a significant delay in diagnosis of celiac disease. However, there is no formula based on hemoglobin or other indices to know when the clock begins ticking in order to determine at what point intestinal pathology begins. In other words, there is no evidence here to allow one to calculate how long it took for Petitioner's disease process to cause anemia. And there is no evidence about how long it took for her anemia to progress to severe anemia.

On September 10, 2011, Petitioner had shortness of breath, pain in her legs, and weakness. The experts and medical literature identify shortness of breath as a symptom of iron deficiency anemia. Petitioner's shortness of breath at the cross-country meet on September 10, was more likely than not, a manifestation of her iron deficiency anemia. Petitioner, in her brief, agrees that "the earliest symptoms that could be attributed to celiac disease would be September 10, 2011, when Petitioner reported shortness of breath and leg soreness during the cross-country meet." Pet. Br. at 12. Petitioner continued to have shortness of breath and weakness during subsequent cross-country meets from September 17 through October 4, 2011. Petitioner's history of shortness of breath is corroborated by medical records dated January 5, 2012, when she reported that she had experienced shortness of breath for a couple of months. Therefore, the undersigned finds that Petitioner's shortness of breath described on September 10, 2011, and through October 4, 2011, was the earliest manifestation of her celiac disease. Therefore, the undersigned finds that Petitioner had anemia during the time period of September 10 to October 4, 2011.

The next question is how long it took for Petitioner to develop anemia present between September 10 and October 4, 2011. Dr. Liacouras referenced medical literature that describes the five stages of iron deficiency anemia. However, there was no time frame given for each stage of the process. The article by Zhu et al., provides a diagram showing the decrease in hemoglobin due to iron deficiency in a patient with severe iron deficiency. See Resp. Ex. V, Tab 6 at 4 fig. 1. In that case, it took approximately 10 months for the patient's hemoglobin to significantly decrease. Id. However, this is just one case report, and its findings do not establish any normative value.

In those patients who present with anemia, like Petitioner, Paez et al. reported a mean delay of 3.5 years prior to diagnosis of celiac disease. Other articles referenced by Dr. Liacouras described much longer periods of delay in diagnosis of celiac disease. Dr. Liacouras's opinion that there was more likely than not a delay between onset and diagnosis of Petitioner's celiac disease is reasonable. However, there is no formula that can be applied retroactively to determine whether that period of delay was months or years.

Turning to the causal theories posited by Petitioner, Dr. Lerner did not offer an opinion or supportive evidence about an appropriate onset interval for his mechanisms (alum adjuvant, polysorbate 80, or *S. cerevisiae*). Since there is no evidence of an appropriate temporal association, the undersigned finds there is not preponderant evidence of Althen Prong Three for these theories.

Dr. Shoenfeld offered two opinions about onset, and presumably these relate to his theory based on molecular mimicry. Initially, he opined that Petitioner developed symptoms within weeks of her first HPV vaccination. Later he opined that onset of symptoms was within two months. Regardless, he clearly opined that the onset of Petitioner's celiac disease occurred after her first vaccination on August 30, 2011.

In contrast, Dr. Liacouras opined that Petitioner's onset was prior to her first HPV vaccination. He further opined that it would take six to 12 months for Petitioner to develop severe anemia (resulting in a hemoglobin of 8.7 in January 2012), and that it takes months or years for the symptoms of celiac disease to manifest.

Here, there is no evidence to suggest that Petitioner had an acute event, such as acute bleeding, which caused her hemoglobin to drop precipitously. At the hearing in this matter, both Petitioner and her mother testified that Petitioner's shortness of breath was worse in December 2011 than it had been in September 2011. Based on Petitioner's clinical course described in the medical records, by Petitioner, and by her mother, and informed by the opinion of Dr. Liacouras, the weight of the evidence shows that Petitioner's illness followed a chronic course, consistent with that described in the literature cited by Dr. Liacouras. That Petitioner's course was more slowly progressive and chronic in nature is also consistent with the fact that Petitioner and her mother did not seek medical care in September 2011 when she began to have shortness of breath and problems running. It was not until her shortness of breath (a symptom caused by anemia) became severe that her mother sought medical care.

Dr. Liacouras persuasively explained the clinical course of chronic malabsorption and iron deficiency anemia, which results in a delay before the illness is diagnosed. The undersigned finds Dr. Liacouras' opinions in this respect to be persuasive. While it is not possible to know when Petitioner's disease process began, it is likely that it took a period of time for Petitioner to develop the anemia that caused her to have fatigue in the summer of 2011 and shortness of breath experienced on September 10, 2011 based on the evidence provided. Similarly, it took more time for her anemia to become severe (hemoglobin of 8.7), which occurred by January 5, 2012. This progressive worsening is consistent with the more chronic course described by Dr. Liacouras.

Even if Petitioner's celiac disease presented more acutely, as Petitioner asserts, it is unlikely that an HPV vaccination administered on August 30, 2011 could cause anemia approximately 10 days later, on September 10, 2011 (evidenced by weakness and shortness of breath). Petitioner has presented no evidence that onset of anemia could occur in the span of 10 days.

Dr. Liacouras opines that more likely than not Petitioner's celiac disease began well before the HPV vaccine was first administered on August 30, 2011. The undersigned agrees. It is unlikely that the HPV vaccination could induce celiac disease, through any immune mechanism, and lead to iron deficiency anemia and manifest as weakness and shortness of breath, in a 10-day time frame.

In conclusion, while Petitioner's initial manifestations of celiac disease occurred September 10, 2011, the onset of her illness, more likely than not, began earlier in time, and prior to her first HPV vaccination on August 30, 2011. Therefore, Petitioner has failed to establish by preponderant evidence Althen Prong Three.

VIII. CONCLUSION

Petitioner has experienced significant pain and suffering due to her celiac disease and the undersigned extends her sympathy to Petitioner for the hardships she has experienced. However, the undersigned's Decision cannot be based upon sympathy for the Petitioner but rather an analysis of the evidence and application of the law.

For the reasons discussed above, the undersigned finds that Petitioner has not established by preponderant evidence that she is entitled to compensation and her petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master