In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: September 23, 2024

VICTORIA PUSATERI,	*	
	*	
Petitioner,	*	No. 16-467
	*	
v.	*	Special Master Gowen
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Scott W. Rooney, Nemes, Rooney P.C., Farmington Hills, MI, for petitioner.
Catherine E. Stolar, U.S. Dept. of Justice, Washington, D.C., for respondent.

DECISION[1]

On April 13, 2016, Victoria Pusateri ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program.[2] Petition (ECF No. 1). Petitioner alleges that the human papillomavirus ("HPV") vaccine administered on February 18 and April 22, 2013 significantly aggravated her immunodeficiency disorder, inflammatory bowel condition, esophagitis, bronchitis, and alopecia areata. Petition ("Pet.") at 2-5. Based on a full review of the evidence including medical records and expert reports, I find that petitioner has not established by preponderant evidence that the HPV vaccine caused or significantly aggravated any of her conditions and the petition must be **DISMISSED.**

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this opinion contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the opinion will be available to anyone with access to the Internet.** Before the opinion is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the opinion will be posted on the court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

I. Procedural History

Petitioner filed a petition for compensation on April 13, 2016 and her petition was accompanied by medical records. *See* Pet. Exhibits ("Exs.") 1-10, 12. On December 14, 2017, petitioner filed expert reports from John Santoro, D.O..[3], a gastroenterologist, to support her claim that the HPV vaccines caused petitioner to have ulcerative colitis and Marc David Glashofer, M.D, M.S.[4], to support her claim that petitioner's alopecia was caused by the HPV vaccines. Pet. Exs. 14, 15 (ECF Nos. 57, 59).

Respondent filed the Rule 4(c) report, recommending against compensation, arguing that "the alleged development of petitioner's symptoms is outside the accepted timeframe to demonstrate vaccine causation or significant aggravation," and that petitioner's diagnosis of Common Variable Immune Deficiency ("CVID") and antibiotic use provide alternative causes for petitioner's symptoms. Respondent ("Resp.") Report ("Rept.") at 6-7 (ECF No. 64). Respondent also filed an expert report from Randy Longman, M.D.[5], a gastroenterologist, who opined that petitioner's underlying immune deficiency and repeated exposure to antibiotics caused the exacerbation of her colitis. Resp. Ex. A at 5 (ECF No. 63).

---

[3] Dr. John J. Santoro was a gastroenterologist in practice with Atlantic Gastroenterology. Pet. Ex. 14. He unfortunately passed away during the course of this litigation. Dr. Santoro served as the Medical Director of Clinical Research at Atlantic Gastroenterology Associates and was Director of the Hepatitis Treatment Center at the same group. *Id.* After completing undergraduate at LaSalle College, he attended Philadelphia College of Osteopathic Medicine and graduated in 1978. Pet. Ex. 14A at 2. Dr. Santoro completed a residency at the University of Medicine and Dentistry at John F. Kennedy Memorial Hospital in 1981. *Id.* Dr. Santoro became a Fellow of Gastroenterology at University of Medicine and Dentistry with the NJ School of Osteopathic Medicine and with the Kennedy Memorial Hospitals. *Id.* at 3. He was board certified in Internal Medicine and Gastroenterology. *Id.* Dr. Santoro was licensed to practice medicine in New Jersey and Pennsylvania. *Id.* As of the filing of his CV, Dr. Santoro was a Clinical Associate Professor of Medicine at Rowan University of Osteopathic Medicine. *Id.* at 4. Additionally, Dr. Santoro has authored or co-authored numerous medical articles on issues that affect the gastrointestinal tract. *Id.* Dr. Santoro has provided his opinion in other vaccine cases, where he has been accepted as an expert in gastroenterology. *See e.g. B.E. v. Sec'y of Health & Human Servs.,* No. 15-1458V, 2019 WL 1560371 (Fed. Cl. Spec. Mstr. Feb. 26, 2019). Accordingly, for the purposes of this case, Dr. Santoro is accepted as an expert in gastroenterology for this matter.

[4] Dr. Marc D. Glashofer is a dermatologist in practice with The Dermatology Group in West Orange, New Jersey. Pet. Ex. 15A. He attended the University of Maryland for his undergraduate degree and attended the George Washington University School of Medicine and Health Services in Washington, D.C. *Id.* Dr. Glashofer completed his residency in dermatology at Tulane University School of Medicine in New Orleans, Louisiana. Dr. Glashofer is board certified in dermatology. He serves as a peer reviewer for the Journal of Dermatologic Treatment and Journal of Drugs and Dermatology and is on the Clinical Research Advisory Council for the National Alopecia Areata Foundation. *Id.* at 3. It does not appear that Dr. Glashofer has appeared as an expert in the Vaccine Program before, however, he is a practicing dermatologist with expertise in the field. Accordingly, Dr. Glashofer is accepted as an expert in dermatology in this matter.

[5] Dr. Randy Longman is an assistant professor of gastroenterology and hepatology at at the Jill Robrts IBD Center at Weill Cornell Medical Center in New York. Resp. Ex. B. He received his undergraduate degree from Yale University and then received his medical degree from Cornell Medical College and his Ph.D. in immunology from the Rockefeller University. *Id.* He received his medical degree in 2007 and did his post-doctoral training in Gastroenterology at Columbia Presbyterian Medical Center. *Id.* Dr. Longman completed a gastroenterology fellowship in 2013. He is licensed to practice medicine in the state of New York. He has authored or co-authored numerous medical articles in the field of gastroenterology. *Id.* at 3-5. He is well qualified to provide an expert opinion on gastroenterology and immunology.

The undersigned held a Rule 5 Status Conference on April 25, 2018, when I observed that petitioner had a pre-existing history of alopecia, but that it was possible that the ulcerative colitis may have been caused by an immune reaction to the HPV vaccine. Rule 5 Order at 1-2. I also observed that petitioner had a treating physician from the Children's Hospital of Michigan, indicate that it was a possibility that petitioner had CVID, but thought that petitioner's hypogammaglobulinemia would be reversed once her colitis was under control. *Id.* at 2; *see also* Pet. Ex. 2 at 67.

After both parties filed supplemental expert reports from the gastroenterologists and petitioner filed updated medical records, I held another Rule 5 status conference. *See* Resp. Ex. G; Pet. Ex. 20. I noted that petitioner's diagnosis appeared to be somewhat less clear, especially as her immune deficiency continued, even after her colitis had resolved. Furthermore, I again noted that some of petitioner's medical records suggest that her alopecia, urticaria, warts, and recurrent sinusitis appeared prior to the vaccinations. Rule 5 Order (ECF No. 94). I posed a series of questions to petitioner's experts in the Order.

Petitioner continued to supplement the record with updated medical records, which included diagnoses from treating physicians. *See* Pet. Ex. 25. I held another status conference on January 22, 2020, when I reviewed these records with the parties and observed that petitioner's diagnoses included CVID, alopecia areata, inflammatory bowel disease, and others. Scheduling Order (ECF No. 108). Furthermore, petitioner was also diagnosed with "possible WHIM syndrome,"[6] and chronic urticaria and angioedema. *Id.* at 2; *see also* Pet. Ex. 26 at 2099. During the status conference, petitioner's counsel stated that petitioner was "narrowing" her claim, focusing on a significant aggravation of alopecia. Scheduling Order at 2. I indicated that it would take an additional expert report to "consider how the HPV vaccine stimulated (or significantly aggravated) an autoimmune condition like alopecia if it is clear that petitioner did not mount any immune response to the vaccine, as observed by Dr. Savasan. *Id.* I indicated that the explanations offered by her previous expert, Drs. Santoro and Glashofer, were not supported by the medical records, as petitioner continued to suffer from common variable immune deficiency after her colitis resolved and her alopecia began prior to vaccination. *Id.*

Petitioner filed a supplemental expert report from Alan F. Cutler, M.D., another gastroenterologist. Pet. Ex. 28 (ECF No. 119). Dr. Cutler indicated that he disagreed that petitioner's CVID was caused by intestinal inflammation, but that petitioner developed gastroparesis because of the HPV vaccine. *Id.* at 1-2. I held another status conference with the parties on July 27, 2021, when I recounted petitioner's extensive medical history and indicated that Dr. Cutler's newest opinion that petitioner developed gastroparesis because of the HPV vaccine had significant problems. I noted there was no evidence that petitioner had gastroparesis and by this time petitioner's diarrhea had resolved and her immunoglobulins remained essentially undetectable. While both Drs. Santoro and Cutler focused on Dr. Marks' early

[6] WHIM syndrome is a congenital immune deficiency with characteristics clinical features that include **W**arts, **H**ypogammaglobulinemia, recurrent bacterial **I**nfections, and **M**yelokathexis (apoptosis of mature myeloid cells in the marrow). Kawai, T. and Malech, H., *WHIM Syndrome: Congenital Immune Deficiency Disease*, 16(1) Curr. Opin. Hematol. 20-26 (2009), doi: https://doi.org/10.1097%2FMOH.0b013e32831ac557.

hypothesis that the immune deficiency was caused by her diarrhea, Dr. Marks had appropriately revised her opinion to diagnose agamaglobulanemia not caused by diarrhea.

I recommended that petitioner voluntarily dismiss her petition, however, if petitioner intended to proceed on this matter, I set a deadline for respondent to file a motion to dismiss. Scheduling Order (ECF No. 123).

Petitioner decided to continue to proceed with her claim. In the interim, petitioner's attorney filed a third motion for interim attorneys' fees and costs. *See* Pet. Mot. for Interim Attorneys' Fees and Costs (ECF No. 126). I held another status conference in this matter, when I indicated that "the path to demonstrating entitlement by preponderant evidence seems extremely unlikely in this matter," and the medical records demonstrated that petitioner had no response to the HPV vaccine, or any other vaccines she had received. *Id.* at 2. Accordingly, I requested that petitioner file a voluntary dismissal decision, but that if she continues to proceed, respondent will file a motion for a ruling on the record.

On March 30, 2022, respondent filed a motion for a ruling on the record, requesting that this petition be dismissed. Resp. Motion ("Mot.") (ECF No. 139). Petitioner filed a response to respondent's motion on August 15, 2022. Pet. Response to Mot. (ECF No. 142). On October 6, 2022, respondent filed a reply to petitioner's response. Resp. Reply (ECF No. 144).

This matter is now ripe for adjudication.

II. Evidence Submitted

a. Petitioner's Medical History

i. Medical History Prior to Administration of HPV Vaccine on February 18, 2013

Petitioner was born on October 10, 1997, at 36 weeks of gestation and weighed 5 pounds six ounces. Pet. Ex. 2 at 120. She received her regular vaccines, including varicella, hepatitis B, MMR, TDaP and influenza. *Id.* at 117. In April 2003, petitioner was admitted to the Children's Hospital of Michigan for vomiting and abdominal pain, which was suspicious for a right adrenal mass. *Id.* at 121. During her hospitalization, she was noted to have episodic hypertension. *Id.* Petitioner had a follow-up appointment with Dr. Neena Gupta on June 2, 2003, after the hospitalization, at which she noted that petitioner had an esophagogastroduodenoscopy that showed "mild esophagitis." *Id.* It was thought that petitioner's intermittent blood pressure elevation was due to anxiety, and it was recommended that she have periodic blood pressure monitoring. *Id.* at 122. At a follow-up appointment on July 14, 2003, petitioner's mother indicated that petitioner had been taken off of Zantac, and that petitioner's abdominal pain, nausea, vomiting, and heartburn subsided. *Id.* at 119. It was recommended that petitioner can go back on Zantac if her symptoms flare up again and she can come back to the gastroenterology clinic as needed. *Id.*

Petitioner had a well visit on October 28, 2004. Pet. Ex. 2 at 118. The note from this appointment indicates that she had no speech problem and was doing well in general. *Id.* On November 5, 2004, petitioner had a consultation with Dr. Robert Rhee for a "bump in the corner of her left eye." *Id.* Petitioner had 20/20 vision in both eyes, but she had a fluid-filled cyst in the corner of her left eye. *Id.* Dr. Rhee recommended petitioner to Dr. Christine Nelson at the University of Michigan, an oculoplastic surgeon for evaluation and treatment. *Id.* Later the same month, petitioner had a consultation at the Eye Plastic Orbital and Facial Cosmetic Surgery Clinic at the Kellogg Eye Center. *Id.* at 112. Petitioner was diagnosed with a "probable cystic lesion of the left medial rectus area," and it was recommended that it be removed and biopsied. *Id.* On August 9, 2005, petitioner had the cyst removed from her left eye. *Id.* at 106.

On August 26, 2009, at age 12, petitioner was admitted to the University of Michigan Hospital for a three-day history of frequent vomiting and diffuse, crampy, constant abdominal pain. Pet. Ex. 2 at 95. Prior to admission, petitioner had acute onset of nausea, vomiting and abdominal pain after camping out during a birthday party, where another child also had nausea and vomiting. *Id.* Petitioner was given Visteril, which sedated her, but she continued to vomit afterwards. The vomiting continued for three days, but only slightly less frequently. *Id.* Petitioner had elevated blood pressure and generalized lymphadenopathy. *Id.* at 97. It was suspected that her abdominal pain was likely due to gastroenteritis, but considered a "slightly unusual presentation." *Id.* A pelvic ultrasound showed intra-abdominal lymphadenopathy. *Id.* Petitioner was discharged three days later, with diagnoses that included, "gastroenteritis, intermittent hypertension and generalized lymphadenopathy." *Id.* at 94.

On January 10, 2011, petitioner had an appointment with her pediatrician for a fever and swollen neck. Pet. Ex. 9 at 1. Petitioner reported that her jaw hurt, and her head was congested for a week. *Id.* She was diagnosed with sinusitis and given a prescription for antibiotics. *Id.* Four months later, on April 12, 2011, petitioner was taken back to her primary care for "hives on and off for one week that were on her arms, legs, and torso." *Id.* She was diagnosed with recurrent urticaria and given a course of prednisone and a prescription for Atarax, an antihistamine. *Id.* Approximately two weeks later, on April 25, 2011, petitioner returned to her primary care provider for the continued rash all over her body. *Id.* Petitioner was directed to take Allegra, although her rash was not getting better. *Id.* The note from this appointment indicates that her rash was going on for 3-4 weeks with "no known trigger," and that she did not have exposure to a cat, dog, or have hay fever. *Id.* Petitioner's doctor stated that she should begin prednisone and take Zyrtec and follow-up in 10-16 days. *Id.*

Petitioner returned on May 11, 2011 for the follow-up for her hives, which had gone away and then came back. Pet. Ex. 9 at 2. Petitioner reported that she stayed with her father who has a dog and her hives returned. *Id.* Petitioner was also not taking Zyrtec. She was referred to the allergy clinic at Children's Hospital.

On June 28, 2011, petitioner had an appointment with Dr. Sahar Faghih at the allergy and immunology clinic at Children's Hospital of Michigan. Pet. Ex. 2 at 87. This appointment notes that petitioner was seen previously on May 31, 2011 for "a complaint of chronic urticaria and sinusitis." *Id.* The record indicates that she completed a course of Augmentin which alleviated her nasal congestion and pressure, but the Zyrtec did not "significantly improve the occurrence

of her hives," and that she gets them intermittently. *Id.* Petitioner reported that her hives began while staying with her father who has two dogs. *Id.* She was diagnosed with chronic urticaria and possible dust mite sensitivity. *Id.* Dr. Faghih's plan was to do a skin test at the next appointment. *Id.* However, no further records from Dr. Faghih or the Allergy and Immunology Clinic from this time period were filed.

On October 14, 2011, petitioner received a flu shot. Pet. Ex. 9 at 3. She presented for a sick visit on December 31, 2011 for coughing and green mucus that was present for one week prior to the appointment. *Id.* She was diagnosed with sinusitis and given a prescription for Augmentin and to use a nebulizer at home. *Id.* at 4.

There are limited medical records between 2011 and November 2012, when there is another appointment with her primary care provider, when she reported that her right eye hurt and she noticed that some of her eye lashes were falling out. Pet. Ex. 9 at 5. Petitioner's mother expressed some concern about a thyroid issue. *Id.* Petitioner was given eye drops. She presented again on January 9, 2013, complaining that her right ear was red and painful, and she was coughing constantly. *Id.* at 5. Petitioner was diagnosed with sinusitis and prescribed a course of antibiotics. *Id.* She was told to follow-up in 10-14 days. *Id.* On January 30, 2013, petitioner again reported coughing and congestion. *Id.* The nebulizer did not work and she finished the amoxicillin. *Id.* Petitioner was diagnosed with acute bronchitis and rhinitis and given another prescription for amoxicillin. *Id.* Petitioner returned on February 18, 2013, again with coughing and congestion, this time her voice was hoarse, and her neck felt swollen. *Id.* At this appointment, petitioner wanted to get the HPV vaccine and the vaccine was administered. She was also diagnosed with bronchitis. *Id.*

ii. Interim Medical History Between February 18, 2013 and second HPV Vaccine Administered on April 22, 2013

The next medial appointment in the medical records occurred on April 16, 2013, with Dr. Steven Grekin, a dermatologist. At this appointment, petitioner had a plantar wart on her right foot between the 1st and 2nd toes. Pet. Ex. 4 at 6. Importantly, this was a follow-up appointment which suggests that petitioner had prior appointments with him, however, records from those appointments were not filed.

Petitioner had an appointment on April 20, 2013 for a runny nose, coughing and green discharge for five days. Pet. Ex. 2 at 3. Additionally, petitioner's hives had returned on her arms and legs. *Id.* Petitioner was diagnosed with urticaria and acute bronchitis and rhinitis. *Id.* She was given a course of prednisone and Azithromycin. *Id.* Petitioner returned for her second HPV vaccine on April 22, 2013. *Id.*

iii. Petitioner's Medical History After April 22, 2013 to Present

Seven days after her second HPV vaccination, on April 29, 2013, petitioner returned to her primary care physician for a follow-up of her sinus infection. Pet. Ex. 2 at 3. Petitioner had finished her antibiotic course; however, her hives were now all over her body. *Id.* Petitioner indicated that the hives were coming and going. *Id.* Petitioner also reported that the cough and

congestion was a little better while on the antibiotics, but they came back. *Id.* Claritin and Zyrtec were not helpful in controlling the hives either. *Id.* She was prescribed a fourteen-day course of Augmentin, another antibiotic. *Id.*

Petitioner returned to her pediatrician on May 1, 2013 for a follow-up and she indicated that her hives were improving on the prednisone. Pet. Ex. 2 at 4. Her physician wrote that she was "unable to determine cause of hives since she had been having recurring hives prior to getting both antibiotics." *Id.* at 4.

On June 12, 2013, petitioner had an appointment with her primary care physician for coughing, hives (for three months), eye lashes and eyebrows falling out for two months, and diarrhea for one week. Pet. Ex. 2 at 4. It was noted that petitioner had recurrent hives and that she had an allergy evaluation, and the cause of the hives was undetermined. *Id.* Petitioner was referred to an allergist for another evaluation and diagnosed with recurrent urticaria. *Id.* Two weeks later, petitioner reported that she was still having diarrhea twice a day, her left ear was plugged and she still had hives. *Id.*

On June 28, 2013, petitioner had a follow-up appointment with her dermatologist for the plantar warts. Pet. Ex. 4 at 5. There was a note indicating that petitioner had concerns about her eyelashes and eyebrows falling out for three months. *Id.* Petitioner also reported that she had diarrhea for three weeks and a history of ulcerative colitis. Petitioner was diagnosed with urticaria and alopecia eyebrow. *Id.*

Petitioner had a consultation at the Gastroenterology, Hepatology, and Nutrition Clinic at Children's Hospital of Michigan on July 10, 2013. Pet. Ex. 12A at 22. Petitioner reported that she was having diarrhea for four weeks, up to six times a day, but decreased. *Id.* Petitioner also reported abdominal pain, but the pain resolves once she has a bowel movement. *Id.* As part of her medical history, it was noted that petitioner had chronic urticaria and she had been hospitalized for vomiting when she was five. *Id.* The plan was for comprehensive blood work and an upper endoscopy and colonoscopy. *Id.* at 24. The blood work revealed that petitioner had extremely low levels of IgA and IgE. *Id.* at 32.

On July 15, 2013, petitioner had an appointment with Dr. James Fordyce. Pet. Ex. 2 at 73. The reasons for the visit were "chronic urticaria, rhinitis, ear-infection, and diarrhea." *Id.* She was diagnosed with idiopathic urticaria and chronic ear infections, along with chronic rhinitis. *Id.* at 75. She was going to have her IgG, IgA, IgM, and IgE tested. *Id.* Regarding her diarrhea, Dr. Fordyce considered an inflammatory process, such as Crohn's disease or functional bowel issues. *Id.* Petitioner's blood work showed that she had nearly no IgE, IgA, IgG or IgM. *Id.* at 71.

Petitioner had an endoscopy and colonoscopy on July 18, 2013. Pet. Ex. 2 at 69; Pet. Ex. 12A at 135. The endoscopy revealed a fungal infection in her esophagus, and she was given a prescription for Diflucan. *Id.* The colonoscopy revealed diffuse active chronic colitis. *Id.* at 141. Petitioner had an appointment with gastroenterologist, Dr. Macha on July 24, 2013, to follow-up from the colonoscopy and endoscopy. Pet. Ex. 12A at 145. Dr. Macha explained that petitioner had Candidal esophagitis and inflammatory bowel disease, more likely Crohn's than

ulcerative colitis. *Id.* At a follow-up with Dr. Macha on August 7, 2013, petitioner reported that her diarrhea was improving, and her abdominal pain and nausea had resolved. Pet. Ex. 12A at 190. Dr. Macha ordered repeat blood work.

On August 5, 2013, petitioner had an appointment with immunologist, Dr. Amy Marks in the Department of Allergy, Immunology and Rheumatology at the Children's Hospital of Michigan. Pet. Ex. 2 at 65. Dr. Marks wrote that petitioner was being seen for hypogammaglobulinemia.[7] *Id.* Petitioner reported that her hives began two years prior, and they are chronic but sporadic. *Id.* Petitioner indicated that she was able to treat them with oral antihistamines, but approximately six to eight months ago, the hives worsened. *Id.* at 66. Additionally, petitioner reported a nine-week history of diarrhea. *Id.* Dr. Marks wrote that petitioner had levels of IgA, IgE, IgG, and IgM that were "significantly low." *Id.* Dr. Marks diagnosed petitioner with chronic urticaria, colitis, likely Crohn's disease, hypogammaglobulinemia and truncal esophagitis. *Id.* at 67. Initially, Dr. Marks hypothesized that petitioner's hypogammaglobulinemia was likely secondary to her diarrhea and colitis. *Id.* Because petitioner was being treated with steroids and Asacol, she wanted to retest her immune globulins to see if there was improvement. *Id.* Dr. Marks also wrote that another possibility and cause is CVID, but wrote, "However, at this time, I do believe this is a secondary hypogammaglobulinemia that can be reversed once her colitis is under better control." *Id.* Additionally, Dr. Marks also considered whether petitioner's chronic urticaria could "correlate with an autoimmune disease, like Crohn's," and that petitioner, "likely has autoimmune urticaria." *Id.* at 68. She asked to see petitioner in October. *Id.*

Petitioner had a follow-up with Dr. Marks on September 25, 2013. Pet. Ex. 2 at 55. Petitioner's follow-up blood work once again showed no immunoglobulins, including IgG, IgA and IgM. Pet. Ex. 2 at 55. Petitioner reported that her diarrhea had subsided, but she was beginning to show signs of sinusitis. *Id.* During this visit, petitioner reported to Dr. Marks that she was experiencing "quite severe plantar warts on her right foot, involving four of the five toes," and that she was experiencing flat warts on her face. *Id.* Dr. Marks wrote, "Again, when looking back, the warts also started approximately two years ago, which is when [petitioner] started becoming sick quite regularly with sinus infections, per Mom." *Id.* Dr. Marks recommended that petitioner continue a steroid taper, with her last dose being October 4th. At this appointment, Dr. Marks wrote, "Given this constellation of symptoms, with complete agammaglobulinemia, recurrent infections, and warts, I do have some concerns for WHIM syndrome; however, she does not have the typical variants with abnormalities on CBC and neutropenia that can be seen." *Id.* at 56. Dr. Marks stated that it was "imperative" that petitioner begin IVIG, given the recurrent infections and constellation of findings. *Id.* Dr. Marks opined that petitioner either had "atypical agammaglobulinemia or WHIM syndrome variant." *Id.* Petitioner began receiving IVIG infusions on a monthly basis. *See* Pet. Ex. 17 at 33; Pet. Ex. 5 at 2; Pet. Ex. 26 at 2093.

[7] Hypogammaglobulinemia is abnormally low levels of all classes of immunoglobulins in the blood. *Hyopogammaglobulinemia,* Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24235&searchterm=hypogammaglobulinemia (lasted visited Sept. 22, 2024).

Petitioner returned to Dr. Macha on October 30, 2013 for a re-evaluation. Pet. Ex. 12A at 372. Petitioner's abdominal pain and nausea had subsided. *Id.* Petitioner also was having normal bowel movements and was feeling good after two infusions of IVIG. *Id.* Petitioner was continuing on Asacol and was "clinically doing well." *Id.* A re-evaluation of her GI tract was recommended after she had completed 3-4 months of IVIG treatment. *Id.*

On December 5, 2013, petitioner was evaluated by Dr. Sureyya Savasan, a hematologist in the Department of Hematology and Oncology at the Children's Hospital of Michigan. Pet. Ex. 2 at 49. Dr. Savasan noted that petitioner experienced four to six weeks of diarrhea before going to the Gastroenterology Clinic in July 2013. *Id.* Additionally, she wrote that petitioner has chronic urticaria which started two years ago and plantar warts involving the inner surfaces of her toes for the past two years. *Id.* Further, petitioner reported that she had "a few warts on her face which currently have subsided." *Id.* Petitioner also reported to Dr. Savasan that she had experienced hair loss that begun "one year ago," and mainly involves her scalp hair, eyelashes, and on the upper extremities. *Id.* Petitioner "noticed a distinct area of hair loss on the right side of the scalp on the frontal region" and "there is a discrete area of hair loss on the left forearm which she noticed about five to six weeks ago." *Id.* Under "Past Medical History," Dr. Savasan recorded that petitioner "has a history of recurrent URI infections since childhood and she has been treated with several courses of antibiotics periodically for suspected clinical sinusitis; however, she does not have any documented bacterial or fungal infections." *Id.* Dr. Savasan also observed that petitioner has received all her immunizations, including the two HPV vaccine doses, but "has not mounted an immune response to the vaccines." *Id.* at 51. Dr. Savasan wrote that petitioner had "almost undetectable levels of immunoglobulins, including IgG, IgA, IgM, and IgE, her absolute neutrophil count ranged from 2,700-11,000, and her transaminase levels normalized. *Id.* Dr. Savasan assessed petitioner with hypogammaglobulinemia with chronic IVIG infusions, plantar warts, inflammatory bowel disease, history of candida esophagitis, and alopecia areata. *Id.* at 53. Dr. Savasan opined that a potential diagnosis of atypical WHIM, which was being entertained by Dr. Marks, was suspect because her neutrophil levels were normal and she did not have any serious infections, aside from the repeated upper respiratory infections. *Id.* Dr. Savasan wrote that there needed to be further evaluation of petitioner's "autoimmune/immunodysregulation condition," and that additional labs were being ordered, including T, B and NK cell subset counts, ANA, anti-microsomal antibodies, anti-smooth antibodies, and anticardiolipin antibody screen "due to the co-existence of immunodeficiency and autoimmunity and her clinical spectrum." *Id.* at 53.[8]

On December 30, 2013, petitioner returned to Dr. Marks for a re-evaluation of her hypogammaglobulinemia. Pet. Ex. 2 at 39. Petitioner reported that she was no longer having diarrhea, but some constipation. *Id.* Petitioner's IgG levels were improved, though not normal, and she was cleared for a repeat colonoscopy in February. *Id.* Dr. Marks wrote that the antibody tests ordered by Dr. Savasan may not be significant because petitioner does not produce antibodies. *Id.* Dr. Marks also prescribed petitioner cefdinir for 10 to 14 days to combat acute sinusitis. *Id.* at 41.

[8] It was not clear if these tests were ever done as no additional records with Dr. Savasan were filed, despite having a follow-up appointment recorded in other medical records. *See* Pet. Ex. 2 at 42 (noting that petitioner had a follow-up appointment with Hematology/Oncology on January 16, 2014).

Petitioner had an appointment with dermatologist, Dr. Laurie Kohen at the Henry Ford Hospital on January 3, 2014. Pet. Ex. 6 at 2. Petitioner's "History of Present Illness" noted that petitioner had warts on her right foot "ongoing for last 2 years," and had "numerous liquid nitrogen cryotherapy treatments over the years without improvement." *Id.* Petitioner reported a "3-month history of patch of hair loss on her right frontal scalp without associated erythema or pruritus," and that she had eyelash and eyebrow hair loss. *Id.* Dr. Kohen wrote that petitioner "has been undergoing significant medical stressors as she is being worked up for an immunodeficiency disorder due to findings of absent immunoglobulins all of which began with a several week history of diarrhea." *Id.* A "well-demarcated area of nonscarring alopecia measuring 4.5 x 3 cm" was located on her right frontal scalp, she also had nonscarring alopecia on her left eyebrow and left forearm. *Id.* at 5. Petitioner also had multiple verrucous papules in the web spaces on her right foot. *Id.* Petitioner received a Kenalog injection in her scalp and eyebrow to treat the alopecia. *Id.* Petitioner was also referred to Dr. Nydorf for bleomycin injections for the verrucae. *Id.*

Petitioner had a follow-up appointment with dermatologist, Dr. Kohen, on February 12, 2014. Pet. Ex. 6 at 7. Petitioner reported that she had one "enlarging lesion on her frontal scalp and a smaller patch adjacent to the larger one," and that she had yet to use topical steroid on her scalp. *Id.* She noted new hair growth in her left eyebrow, but her right eyebrow was now losing hair. *Id.* Dr. Kohen administered another Kenalog injections for the scalp lesions and eyebrow hair loss. *Id.* at 7.

On March 3, 2014, petitioner had a follow-up appointment with Dr. Marks. Pet. Ex. 2 at 35. Dr. Marks's diagnosed petitioner with "primary immune deficiency agammaglobulinemia and chronic urticaria angioedema-autoimmune type." *Id.* at 37. Petitioner was to continue IVIG infusions and continue to be treated by Dr. Kohen for her dermatological issues. *Id.* On March 25, 2014, petitioner underwent a follow-up colonoscopy and endoscopy. *Id.* at 26. Dr. Macha wrote the "EGD demonstrated basal cell hyperplasia in the esophagus and chronic inactive gastritis in the stomach," and the colonoscopy demonstrated "chronic enteritis, chronic colitis with moderate to severe activity in the cecum and ascending colon, and chronic colitis in the transverse colon." *Id.* Petitioner reported no diarrhea, but reduced bowel movements. *Id.* at 25. Dr. Macha diagnosed petitioner with pancolitis that was clinically stable, and that petitioner should continue Asacol twice daily. *Id.* at 27.

On June 25, 2014, petitioner had a follow-up with the gastroenterology clinic at Children's Hospital of Michigan. Pet. Ex. 2 at 25. Petitioner reported that she was eating a regular diet and was not experiencing any abdominal pain, although she expressed some delayed bowel movements. *Id.* It was recommended that petitioner continue Asacol twice daily and to follow-up in four months. *Id.* at 27.

Petitioner had a consultation at the Cleveland Clinic on July 23, 2014 with Dr. Joan Tamburro. Pet. Ex. 5. It was noted that petitioner experienced 12 weeks of diarrhea and it was initially thought that she had Crohn's. *Id.* at 3. Petitioner was experiencing hair loss for 9 months, but her hair loss started prior to the onset of the agammaglobulinemia. *Id.* The hair loss began on her eyelashes, then progressed to her scalp, arm hair, and eyebrows. *Id.* Dr. Tamburro noted that petitioner was receiving Kenalog injections by Dr. Kohen and using Lidex and

Rogaine. *Id.* Dr. Tamburro also noted that petitioner had been diagnosed with "alopecia totalis." *Id.* Additionally, Dr. Tamburro wrote that petitioner had flat warts on her face that were spreading. *Id.* Dr. Tamburro diagnosed petitioner with alopecia areata, verruca plana, verruca vulgaris, and wrote, "Likely related to agammaglobulinemia or other immune differential (immunology considering other diagnoses)," and that she would contact Dr. Marks. *Id.* at 3. Dr. Tamburro had a phone call with petitioner's mother and Dr. Marks and indicated that a follow-up would be beneficial. *Id.* at 8.

On August 27, 2014, petitioner was seen by Dr. Brian Berman at the Hematology Clinic at Beaumont Hospital for the possibility evaluation of "possible emerging leukopenia/neutropenia." Pet. Ex. 3 at 4. Dr. Berman wrote:

> [petitioner] was well until about three years ago when she began to develop recurrent sinusitis. She received multiple antibiotics and never required hospitalization. At some point thereafter, she developed a few months of non-bloody diarrhea and substantial weight process and was placed on Asacol for many months. Her gastrointestinal symptoms ultimately resolved. About a year ago, she was started on monthly IVIG infusions because of very significant hypogammaglobulinemia. Subsequently she has developed widespread alopecia…In addition, she has developed flat warts on her hand as well as feet.

Id. Dr. Berman wrote that "there is a possibility that she has the WHIM syndrome-warts, hypogammaglobulinemia, bacterial infections, and myelokathexis. There is also concern that this may be a variant of common variable immunodeficiency." *Id.* He explained, "Over the last number of months, her blood cell count has been in the 4,000 range with the lowest white count at 3,300 with an ANC of 1700. Because of the association of neutropenia with WHIM syndrome, we've been asked to evaluate the [petitioner]." *Id.* Dr. Berman reviewed petitioner's labs and noted that her current white blood cell count and neutrophils are adequate and that no interventions are necessary at this time. *Id.* at 5. His assessment was:

> 16 y.o. female with B-cell immunodeficiency, with a history of presumed autoimmune alopecia and transient inflammatory bowel process associated with propensity toward papilloma virus. Based on my review of the literature, the possibility of WHIM syndrome seems very real. Not present is the persistent neutropenia usually associated with this syndrome (which is related to myelokathexis-apoptosis of [nature] myeloid cells in the marrow. However, syndromes of this sort may be quite variable in phenotypic expression.

Id.

On September 22, 2014, petitioner returned to the Cleveland Clinic for a follow-up and re-evaluation of her alopecia. Pet. Ex. 5 at 11. Dr. Bayart assessed petitioner with alopecia areata and wrote that "alopecia areata has an unpredictable course, often characterized by periods of hair loss and regrowth," and suggested avoiding immunosuppressive therapies if possible. *Id.* Dr. Bayart also wrote, "Alopecia areata can be triggered by vaccines (such as Gardasil), but usually would occur in closer proximity to the vaccination [than] [petitioner's] alopecia." *Id.*

Petitioner continued to receive monthly infusions of IVIG and had follow-up appointments for alopecia, warts, and gastrointestinal issues. *See* Pet. Ex. 17 at 10. A follow-up appointment with Dr. Marks on September 26, 2016 indicated that petitioner had one sinus infection and a follow-up colonoscopy showed no abnormalities. *Id.* at 33. Petitioner reported that she was having "significant hair growth" and that her plantar warts had improved. *Id.* Dr. Marks' impression was "19-yo with significant immunodeficiency, agammaglobulinemia, concern for WHIM syndrome variant, chronic urticaria," and the plan was for petitioner to continue to receive monthly IVIG infusions. *Id.* at 35. Regarding petitioner's chronic urticaria, Dr. Marks wrote that she reviewed the pathophysiology and characterized it as "autoimmune in nature." *Id.*

On April 21, 2017, petitioner had an appointment with Dr. Michael Cannon. Pet. Ex. 22 at 2. He recounted her medical history, noting that she was diagnosed with ileocolonic Crohn's disease in 2013 and agammaglobulinemia. *Id.* Petitioner also reported that "all of her symptoms of hair loss started after the second inoculation for HPV," and that a "Consultation at Cleveland Clinic was not definite for a true association with the vaccine." *Id.* Dr. Cannon noted that petitioner "chronic urticaria starting five years prior." *Id.* At the time of the appointment, petitioner was experiencing diarrhea, bloating, and cramping. *Id.* Dr. Cannon noted that petitioner's symptoms "completely resolved on budesonide," [9]and he wanted to wean her off of it. *Id.*

Petitioner transferred dermatology care to Dr. Wendy Sadoff and was assessed for alopecia and plantar warts. Pet. Ex. 24 at 1. Dr. Sadoff wrote, "This is a 19-year-old female who comes in for a chief complaint of skin lesions, located on the face. The lesions are flat warts and mild in severity." *Id.* Dr. Sadoff removed the flat warts and gave petitioner cream for her face. *Id.* Petitioner continued treatment through 2017 Dr. Sadoff. On June 9, 2017, Dr. Sadoff removed lesions on the right side of petitioner's face. *Id.* at 5. The records indicate that petitioner continued with Dr. Sadoff through 2019 for treatment of both flat warts and alopecia. *See generally* Pet. Ex. 24.

On December 17, 2018, petitioner had an appointment with gastroenterologist, Dr. Jared Bortman after her hospitalization for viral myocarditis where she was also found to be *c.diff* positive, but negative toxin Pet. Ex. 22 at 18. Petitioner was treated with antibiotics and her diarrhea and abdominal pain resolved and she was also taking budesonide. *Id.* Dr. Bortman noted that petitioner was taking budesonide every other day and for most of 2018. *Id.* After reviewing her history and performing an exam, he wrote that petitioner was "treated for C.diff diarrhea with Vanco x 2 weeks in 7/2018. Clinically resolved. I am curious as to whether she truly has Crohn's disease….Will try to taper off of budesonide." *Id.* at 20.

On May 31, 2019, petitioner sought a second opinion from Dr. Carl Lauter. Pet. Ex. 25 at 20. Dr. Lauter wrote that petitioner has a history of IBS, alopecia and agammaglobulinemia and sought a second immunology opinion and to establish care at the immunology clinic at the Beaumont Hospital. *Id.* He wrote that petitioner was in good health in 2013, except for occasional URIs, isolated congenital cyst removed from the left medial eye corner a wart removed from her foot. *Id.* He also noted that petitioner had hives five years prior to 2013 and

[9] Budesonide is steroid used to treat Crohn's Disease

it was "attributed to heat and sweating." *Id.* Dr. Lauter wrote "she had first shot of HPV in 2/2013. In April 2013 she began having upper respiratory symptoms and hives. Two days later she received her 2nd dose of HPV vaccine and 3 days later developed bronchitis, rhinitis, sinusitis, hives, and swollen fingers. She did not get her 3rd dose of HPV vaccine due to her "reactions." *Id.* Dr. Lauter also wrote that "Her hives were attributed to a possible reaction to Augmentin, however, a month later she continued to have the same symptoms along with loss of her hair, eyebrows, eyelashes, left ear pain and plugging and new onset of non-bloody diarrhea." *Id.* Regarding her alopecia, Dr. Lauter wrote "[petitioner] denies that her diagnosis was confirmed as "alopecia areata," and that she had stopped injections after her hair returned, but she developed a bald spot in November 2018. *Id.* at 21. Dr. Lauter observed that petitioner is followed by Dr. Berman for her thrombocytopenia. *Id.* He diagnosed her with agammaglobulinemia, CVID, viral warts, alopecia areata, thrombocytopenia, IBS (unspecified), and others. *Id.* at 26. He "agreed with current total management including monthly IVIG," and recommended that petitioner do an HPV vaccine test and if negative, complete the HPV series. *Id.* Dr. Lauter also wrote that he agrees "with referral to NIH or other major academic center that has the ability to evaluate complex immune and genetic disorders, such as National Jewish, Mayo Clinic, University of Cincinnati Children's Hospital to assess case more thoroughly." *Id.*

At a follow-up appointment with Dr. Sadoff, petitioner reported that she was again experiencing hair loss, however, her verrucous lesions on her face have completely resolved. Pet. Ex. 24 at 40. Dr. Sadoff noted that Dr. Lauter suggested petitioner participate in an NIH trial. *Id.*

Petitioner saw gastroenterologist Dr. Michael Cannon on June 27, 2019 with complaints of diarrhea. Pet. Ex. 22 at 9. Petitioner reported that she had weaned off budesonide for approximately 6 months and was doing well until she began to have increased bowel movement and watery stools. *Id.* Petitioner restarted budesonide and had "minimal improvement." *Id.* Petitioner was positive for alopecia, sinus drainage, and rhinorrhea. *Id.* Dr. Cannon diagnosed petitioner with "diarrhea of presumed infectious origin." Petitioner was positive for c.diff and PCR toxin. *Id.* at 21. He also wrote that he was "in doubt of the diagnosis of Crohn's disease," and that "Agammaglobulinemia does also put her at risk of infectious etiologies, most notably small intestinal bacterial overgrowth." *Id.* Petitioner was to start a course of cephalosporin for her sinus infection and Dr. Cannon wrote that, "It will be interesting to see if it helps the diarrhea symptoms." *Id.*

Petitioner had a follow-up appointment with Dr. Cannon on September 18, 2019. Pet. Ex. 22 at 4. At this appointment, petitioner reported that she was treated with Vancomycin after testing positive for c.diff. *Id.* Petitioner indicated that she could have up to three days a week where she experienced diarrhea five times a day. *Id.* Petitioner was diagnosed with "diarrhea of presumed infectious origin," and "indeterminate colitis," along with CVID and alopecia. *Id.* at 7. Dr. Cannon wrote, "last colonoscopy in 2016 was completely normal including small intestine. I am in doubt of the diagnosis of Crohn's disease. Agammaglobulinemia does also put her at risk of infectious etiologies; most notably small intestinal bacterial overgrowth. She unfortunately developed c.diff after [antibiotic] treatment."

The most recent medical records filed by petitioner indicate that she was still receiving IVIG infusions at Royal Oak Hospital in March 2020 *See* Pet. Ex. 27.

b. Expert Opinions

i. Petitioner's Expert, Dr. Marc Glashofer's Opinion

Dr. Marc Glashofer, offered his opinion as to how the HPV vaccine could cause a significant aggravation of alopecia in the petitioner. Pet. Ex. 15. He stated that alopecia areata is an autoimmune condition in which "an immune response to a component of the hair follicle leads to loss of hair." *Id.* at 4. He wrote that "There is no universally accepted cause, and no definitive treatment." *Id.*

Dr. Glashofer wrote that the purpose of vaccines is to "induce immunity by stimulating a low-level immune response, such that a subsequent exposure to that immunogen allows the body to recognize the threat and neutralize it with a robust response, thereby minimizing the deleterious effects of the microorganism." *Id.* He stated that during immunization, "there is the potential that a portion of the foreign immunogen introduced may have a similar peptide sequence or be structurally similar to a component of oneself," and that this leads to "the body creating an immune response, not just to the introduced antigen, but to normal components of one's self, thereby leading to autoimmune reactions and disease states." *Id.* at 4-5. Essentially, he endorsed a theory of molecular mimicry, pursuant to which components of the HPV vaccine share homology between the structure of hair follicles. He theorized that the immune response to the vaccine began to target hair follicles, thus exacerbating petitioner's alopecia.

Dr. Glashofer referenced an article by Chu et al., to support his opinion that a vaccination can induce alopecia areata. Pet. Ex. 15 at 4. The article is a case report of a young child who experienced alopecia one week after receiving the third dose of the Japanese encephalitis vaccine and then again three days after receiving the influenza vaccine. Pet. Ex. 15B at 1.[10] The authors of the article wrote that a review of VAERS case reports found "that patients with the zoster vaccination or quadrivalent human papillomavirus vaccination had a greater risk of developing alopecia than unexposed individuals, although the investigators did not have sufficiently detailed clinical information in either study to ascertain whether each case of "alopecia" was alopecia areata." *Id.* The authors hypothesized that an inflammatory response to the vaccine antigens and adjuvants could evoke T-cell mediated immune reactions, which can trigger alopecia areata in genetically predisposed individuals. *Id* at 2. With respect to the case they were describing, the authors wrote, "The occurrence of alopecia areata one week after vaccination followed by regrowth followed by recurrence three days after a different vaccine strongly suggests a link between vaccination and the onset of alopecia in this child, who was probably genetically predisposed." *Id.*

[10] Chu, Chien-Ho, *Alopecia Areata after Vaccination: Recurrence with Rechallenge*, 33 Pediatric Derm. E218-19 (2016). [Pet. Ex. 15B].

Dr. Glashofer also referenced an article by Geier and Geier,[11] which examined autoimmune adverse events after HPV vaccination as evidence that alopecia areata can be caused by the vaccine. The Geier article found that the incidences of "serious autoimmune adverse events," including alopecia, "were significantly more likely," to occur in individuals who received the HPV-4 vaccine than controls. Pet. Ex. 15C. Geier stated that while the etiology of autoimmune disease is "still not completely clear… genetic, immunological, hormonal, and environmental factors are considered to be important triggers," and that environmental triggers can include, bacterial, viral or parasitic infections. *Id.* Furthermore, Geier stated that bacterial, viral, or parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry….it was suggested that the same mechanisms that act in infectious invasion of the host apply equally to the host response to vaccination." *Id.* at 1. The study indicated that the time between vaccination and onset of symptoms of the adverse autoimmune event was 6 to 55 days. *Id.*

Dr. Glashofer concluded his report, stating that "Based on the temporal relationship between the vaccination and the development of the petitioner's signs and symptoms of the disease, there exists a logical sequence of cause and effect, showing that the vaccine resulted in the petitioner's injuries." Pet. Ex. 15 at 4. He wrote that "there are no other non-vaccine factors," which appeared to have played a role. *Id.*

ii. Petitioner's Expert, Dr. Santoro's Opinion

In his first report, Dr. Santoro wrote that petitioner developed diarrhea within one month after receipt of the second HPV vaccination. Pet. Ex. 14 at 6. He stated that petitioner's initial diarrhea was caused by the innate immune response, which failed to resolve and progressed to inflammatory bowel disease, as a result of the later adaptive immune system response. *Id.* at 7. Dr. Santoro explained that inflammatory bowel disease is an immune mediated chronic intestinal condition that can be caused by a combination of factors, including genetics, the environment, and an overreactive immune system. *Id.* at 5. Dr. Santoro wrote that there are several case reports of ulcerative colitis after Gardasil vaccination, which is also an immune mediated chronic intestinal condition. *Id.* He noted that in *Morgan v. Sec'y of Health & Human Servs.,* "the special master found that the petitioner and her experts presented a reasonable theory invoking the role of both the initial innate response to the vaccine antigen (Gardasil) and of the adaptive non-specific response as contributing to the development of ulcerative colitis." *Id.* at 6; *see also Morgan v. Sec'y of Health & Human Servs.,* No. 13-529V, 2015 WL 9694667 (Fed. Cl. Spec. Mstr. Dec. 10, 2015).

Dr. Santoro endorsed a theory of molecular mimicry as a cause of autoimmune disease post-vaccination. Pet. Ex. 14 at 5. He explained molecular mimicry in general terms, stating, "Molecular mimicry is one mechanism by which infectious agents (or other exogenous substances such as vaccines) may trigger an immune response against autoantigens….Molecular mimicry occurs when a pathogen expresses a protein that is remarkably similar in sequence or shape to a protein in the host but sufficiently different to provoke an immune response. This can

[11] Geier, D. & Geier, M., *A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events,* 34(7) Clin. Rheumatol. 1225-1231 (2014). [Pet. Ex. 15C].

lead to the body creating an immune response...to normal components of one's self, thereby leading to an autoimmune reaction and disease." *Id.*

In his second report, Dr. Santoro again wrote that the petitioner was "in excellent health prior to receiving her first Gardasil vaccination on 2/18/2013. Petitioner received her second HPV4 vaccination on 4/22/2013," and then developed generalized urticaria, bronchitis, rhinitis and finger swelling necessitating systemic corticosteroids and within one month of the vaccines developed diarrhea, and ultimately was diagnosed with inflammatory bowel disease." Pet. Ex. 20 at 1. He acknowledged that petitioner had significantly low IgA, IgE, IgG, and IgM, which "would weigh against an excessive auto-immune response," but opined that petitioner's hypogammaglobulinemia was secondary to her severe diarrhea and ulcerative colitis. *Id.*

Dr. Santoro wrote, "If [petitioner] had genetic IgG deficiency, she would have had a long history of bronchitis, pneumonia, ear infections, and sinusitis, which is common with such a deficiency. I did not see any extraordinary such reporting of these problems in [petitioner's records]." *Id.* at 2. He also stated that a review of petitioner's records did not show that she had a history of diarrhea, chronic dermatitis, allergic rhinitis, and recurrent infections, thus he did not believe petitioner had an IgM deficiency prior to receiving the HPV vaccines. *Id.* Dr. Santoro wrote, "hypogammaglobulinemia…can be seen in patients with inflammatory bowel disease, both Crohn's disease and ulcerative colitis." *Id.* at 3. He referenced an article by Elson et al., which examined two patients who developed hypogammaglobulinemia secondary to Crohn's disease. Pet. Ex. 21.[12] The authors acknowledged that "protein-losing enteropathy can be associated with Crohn's disease," but noted that, "this was not the mechanism of hypogammaglobulinemia in these cases." *Id.* at 6. The authors instead found that the patients' hypogammaglobulinemia was T-cell suppressor mediated, meaning that the T-cells inhibited the antibody synthesis. *Id.*

Dr. Santoro stated that petitioner's treating physician, Dr. Marks, "clearly stated that the petitioner had ulcerative colitis that explained her low immune globulin levels after the onset of [petitioner's] ulcerative colitis." Pet. Ex. 20 at 3. Dr. Santoro rejected respondent's expert's opinion that petitioner had Common Variable Immune Disorder ("CVID"), stating that Dr. Marks did not believe that petitioner had CVID, and asserted that petitioner's IgG levels improved after several rounds of IVIG and resolution of her gastrointestinal issues. *Id.* Dr. Santoro stated that "petitioner does not have a general immunodeficiency disorder or CVID," and that it was his opinion that petitioner's active colitis and diarrhea was the cause of petitioner's low levels of immunoglobulins. *Id.*

iii. Petitioner's Expert, Dr. Alan Cutler's Opinion

Petitioner also filed an expert report from another gastroenterologist, Dr. Alan Cutler. Pet. Ex. 28. Taking a different view as to diagnosis from that of Dr. Santoro, or any of petitioner's treating physicians, Dr. Cutler opined that the HPV vaccine caused petitioner to have gastroparesis, which led to erosive esophagitis. *Id.* at 3. He stated that without the HPV vaccine, petitioner "would likely not have developed her upper gastrointestinal symptoms." *Id.*

[12] Charles O. Elson, et al., *Hypogammaglobulinemia Due to Abnormal Suppressor T-Cell Activity in Crohn's Disease*, 86 Gastroenterology 569-76 (1984). [Pet. Ex. 21].

Dr. Cutler also wrote that petitioner was in excellent health prior to the receipt of the HPV vaccine, ignoring the multiple appointments for sinusitis, bronchitis, otitis and coughing prior to the receipt of the first vaccine. He said, "within two months of her HPV vaccine, the petitioner developed a systemic inflammatory reaction including urticaria, bronchitis, rhinitis, distal extremity edema, and subsequent inflammatory bowel disease." *Id.* at 2. He stated, without citation to the record, that, "petitioner describes stomach problems starting in late February 2013," and that she had significant weight loss, reported as 30 pounds, leading to an investigative endoscopy and colonoscopy which revealed severe erosive esophagitis with candida and diffuse active chronic pan-colitis. *Id.* Dr. Cutler wrote that, "The presentation of significant weight loss with severe esophagitis is commonly seen in gastroparesis, which I believe contributed to the patient's presentation and illness." *Id.* He explained that gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of mechanical obstruction. Presenting symptoms include bloating, nausea, emesis, early satiety and epigastric discomfort and pain.

Dr. Cutler wrote that he disagreed with Dr. Marks' finding that petitioner had CVID caused by intestinal inflammation. Pet. Ex. 28 at 2. Although, he did not discuss the consistent findings of essentially nondetectable levels of IgG, IgM, IgA and IgE even well after the diarrhea had ended.

Dr. Cutler explained that gastroparesis presents with symptoms including bloating, nausea, emesis, feeling full, and epigastric discomfort or pain. *Id.* at 2. He stated that causes include, diabetes, autoimmune, post-surgical, viral, neurological disease, or medication induced. *Id.* Similarly to Dr. Santoro, Dr. Cutler opined that molecular mimicry could cause petitioner's gastrointestinal issues though he diagnosed gastroparesis, writing, "There is a cross-reaction from a component of the vaccine which results in the loss of immune tolerance and thereby inappropriate activation of the immune system cells and resulting damage to the gastrointestinal system. An enteric neuropathy develops due to inflammation and immunologic insult to the autonomic nervous system." *Id.* at 3. He also stated that the adjuvant in the HPV vaccine could be the cause of the autonomic nervous system insult, instead of just the antigen in the vaccine. *Id.* at 2.

Referencing an article by Palmieri et al., which examined reports of neuropathy with autonomic dysfunction after HPV vaccination, Dr. Cutler asserted that the adjuvant in the HPV vaccine can cause an autoimmune/inflammatory syndrome induced by adjuvants often referred to as ASIA. *Id.*; Pet. Ex. 30.[13] The authors explained that an adjuvant is designed to enhance an immune response to a vaccine, but the theory proposes that the "adjuvants themselves include some pathogen-associated molecular patterns and/or create a mild tissue injury exposing some damage-associated molecular patterns, which are recognized by the innate immune system through specific pattern recognition." Pet. Ex. 30 at 5. It is the immune response to both the adjuvant *and* the antigen that may cause an autoimmune reaction. *Id.* In their case review, the Palmieri authors found that many patients reported an "acute phase" of post-vaccination

[13] Beniamino Palmieri et al., *Severe Somatoform and Dysautonomic Syndromes after HPV Vaccination: Case Series and Review of Literature*, 65 Immunol. Res. 106-16 (2017). [Pet. Ex. 30].

symptoms, which include low-grade fever, skin rashes, muscle pain, headache, and sensorial disturbances. *Id.* The acute phase onset occurred within hours or days post-vaccination, but then subsided and patients then began experiencing recurrent or chronic symptoms. *Id.* The authors explained that some other studies speculated that post-vaccination fibromyalgia, POTS or complex regional pain syndrome, might be due to dysfunction in the sympathetic nervous system caused by the HPV vaccine in susceptible individuals. *Id.* at 8. Dr. Cutler stated that, "such an event would explain the development of gastroparesis post-HPV vaccination." Pet. Ex. 28 at 3.

Dr. Cutler also referenced an article by Brinth et al., as evidence for causation between the HPV vaccination and the immunologic insult to the autonomic nervous system, including gastroparesis. Pet. Ex. 28 at 3. In the Brinth article, the authors examined autonomic functions of patients who had reported autonomic dysfunction symptoms within the first two months of receiving the HPV vaccine. Pet. Ex. 33.[14] They found 53 patients who reported headache, excessive fatigue, cognitive dysfunction, and widespread neuropathic pain. *Id.* The authors diagnosed over half of the patients with POTS, but explained that POTS "should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own." *Id.* While the authors found "a close chronological association to the vaccination," they did not opine as to how the vaccine could have caused these symptoms in the patients. *Id.*

iv. Respondent's Expert, Dr. Randy Longman's Opinion

Dr. Longman wrote two reports for respondent. Resp. Exs. A & G. His reports focused on both of petitioner's alleged injuries-an aggravation of her alopecia and the cause of her gastrointestinal injury.

Dr. Longman responded to Dr. Glashofer's report, stating, "given the underlying immune deficiency and hypogammaglobulinemia," in petitioner, "Gardasil stimulation of immune-mediated molecular mimicry as suggested by Dr. Glashofer is less likely." Resp. Ex. A at 4. Dr. Longman accepted Dr. Glashofer's explanation of molecular mimicry and wrote that molecular mimicry has been "described to lead to specific autoantibody response to nerve proteins leading to Guillain-Barré syndrome." *Id.* However, "given the [petitioner's] primary immunodeficiency and lack of sustained titers to HBV immunization, it would be more reasonable to suspect a decreased immune response to Gardasil vaccination rather than stimulating cross-reactive autoimmune antibodies." *Id.* at 4.

Dr. Longman explained that CVID is a primary immunodeficiency characterized by impaired antibody production and it is the second most common immunodeficiency. Resp. Ex. A at 3. Clinically, CVID is defined by reduced or absent serum concentrations of IgG, IgA, and IgM. *Id.*; Resp. Ex. G at 2. He wrote that the designation "variable" refers to a heterogenous group of clinical manifestations including recurrent infections, chronic lung disease, and common gastrointestinal diseases. *Id.* The hallmark of CVID is the abnormalities in B cell maturation and differentiation into antibody producing plasma cells. Resp. Ex. G at 2.

[14] Louise Brinth et al., *Suspected Side Effects to the Quadrivalent Human Papilloma Vaccine,* 62 Dan. Med. J. 1-5 (2015). [Pet. Ex. 33].

He explained that "IgM is the initial version of the antibody created by the immune system during the first exposure to antigen." *Id.* As the affinity in the antibody is refined, the antibody type will switch over from IgM to IgG….Low levels of antibodies can result either from impaired production or increased loss of antibodies. Resp. Ex. G at 1. Impaired production generally results from abnormalities in B cell maturation and differentiation into memory B cells that produce antibodies. *Id.* Hypogammaglobulinemia can also occur due to kidney disease, burns, or intestinal inflammation. However, in petitioner's case, even after her inflammatory colitis resolved, petitioner was still presenting with nearly absent or no antibodies of any class. *See* Pet. Ex. 2 at 55-56; Resp. Ex. G at 1.

Dr. Longman explained that petitioner's presentation of diarrhea which ultimately led to her diagnosis is consistent with a CVID presentation. He explained that diagnosis is often delayed following symptom onset. Resp. Ex. A at 5. He referenced and article by Khodadad et al. article which examined gastrointestinal manifestations in patients with CVID and noted that, "Some patients [with CVID] may present with GI problems as their first clinical presentation." Resp. Ex. D at 5.[15] Additionally, the authors stated, "Between 20% and 60% of individuals develop diarrheal disease, and chronic watery diarrhea is common in CVID." *Id.* The authors noted that "inflammatory bowel diseases appear to occur with increased frequency in patients with CVID," but that CVID-associated colitis is "felt to be separate from classic [irritable bowel disease]." *Id.* at 5.

Additionally, an Dr. Longman cited to an article by Cunningham-Rundles and Bodian which explained that the "clinical spectrum of CVID is quite broad, and symptoms of antibody deficiency may not become obvious until young, middle, or even late in life." Resp. Ex. I at 1.[16] Some patients with CVID may present with classic or, more often, atypical inflammatory gastrointestinal disease, resulting in diarrhea, malabsorption and weight loss. *Id.* Furthermore, the article explained, "For unknown reasons, autoimmune diseases, particularly autoimmune thrombocytopenia, rheumatoid arthritis, and pernicious anemia, are relatively common in this patient group." *Id.* Acute, chronic, or recurrent infections were found in almost all the cases of CVID reported in the Rundles and Bodian article, and "almost all the patients had a history of recurrent episodes of bronchitis, sinusitis, and/or otitis." *Id.* at 2.

Dr. Longman observed that petitioner's treating physician, Dr. Marks, initially hypothesized that petitioner's hypogammaglobinemia was related to her active colitis, but noted that these numbers needed to be reversed once her colitis resolved. *See* Pet. Ex. 2 at 64. Importantly, at petitioner's second appointment with Dr. Marks on September 25, 2013 after her diarrhea had resolved and she still had "no immunoglobulins, including IgG, IgA, as well as IgM," and petitioner's mother revealed that petitioner had a two year history of chronic sinus infections, Dr. Marks revised her opinion and diagnosed petitioner with a primary immunodeficiency of "atypical agammaglobulinemia or WHIM syndrome variant." Pet. Ex. 2 at 57; Resp. Ex. G at 1. Dr. Longman stated that Dr. Mark's initial assessment of petitioner was

[15] Ahmad Khodadad et al., *Gastrointestinal Manifestations in Patients with Common Variable Immunodeficiency,* 52 Dig. Dis. Sci. 2977-2983 (2007). [Resp. Ex. D].

[16] Charlotte Cunningham-Rundles and Carol Bodian, *Common Variable Immunodeficiency: Clinical and Immunological Features of 248 Patients,* 92 Clin. Immunol. 34-48 (1999). [Resp. Ex. I].

reasonable and after subsequent evaluation, petitioner's disease was more consistent with a primary immune deficiency and was treated as such with IVIG therapy. Resp. Ex. G at 2.

Dr. Longman also observed that petitioner's experts failed to acknowledged petitioner's medical history, which included repeated sinus infections treated with antibiotics, chronic urticaria, and warts. Resp. Ex. G at 2. In his first report, Dr. Longman reviewed petitioner's medical history in detail, chronicling the appointments where petitioner was treated for repeated sinus infections and recurrent urticaria with antibiotics and steroids. Resp. Ex. A at 1-2. He opined that the delay in diagnosis, the presentation of petitioner with diarrhea, and the repeated sinus infections, are all consistent with a primary immunodeficiency, despite no family history of an immune deficiency or identified genetic disorder to account for her primary immune deficiency. Resp. Ex. G at 2.

With respect to Dr. Santoro's opinion that the innate immune system's response to the HPV vaccine triggered petitioner's diarrhea, Dr. Longman stated that "adverse effects of broad systemic cytokine activation would generally trigger the characteristic biology of fever, change in blood pressure, leukocytosis, and elevated acute phrase reactants and a general sense of feeling unwell. These were not present in [petitioner's] case." Resp. Ex. A at 4. Dr. Longman stated that the "non-specific adaptive immune response does not offer a plausible mechanism for specific intestinal inflammation." *Id.* He wrote that, "[Petitioner] tolerated the initial vaccination without evidence of a non-specific inflammatory response." *Id.* He opined that instead of the vaccine at issue in this case, the temporal association of diarrhea with the use of antibiotics for persistent upper respiratory infections and congestion is more plausible as a cause of the diarrhea. *Id.* at 5. He wrote, "GI manifestations including inflammatory colitis commonly occur in individuals with CVID and repeated antibiotic exposure increases the potential for microbial exacerbation of underlying colitis." *Id.*

He concluded his reports, stating "petitioner's presentation is consistent with a primary immune deficiency such as CVID." Resp. Ex. G at 3. Dr. Longman wrote, "CVID is a common primary immune deficiency that can present without family history and is frequently associated with gastrointestinal inflammation. Therefore, it is my opinion that the petitioner has a primary immune deficiency, likely CVID, that is causally linked to her history of intestinal inflammation." *Id.*

III. Applicable Legal Standards

To receive compensation through 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 actually 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).

In the present case, petitioner does not allege a Table injury. Instead, petitioner alleges that she suffered an off-table significant aggravation of her pre-existing alopecia and a new gastrointestinal injury as a result of the receipt of the HPV vaccination on February 18, 2013 and

April 22, 2013. Pet. Response at 21, 26. Thus, petitioner bears the burden of establishing actual causation of the significant aggravation of these conditions.

a. Causation

Because Petitioner does not allege a Table Injury, she must prove a vaccine she received actually caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *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, 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 material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The special master 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).

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met his or her burden of proof. *Andreu*, 569 F.3d at 1380; *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

"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.").

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 973 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g*., *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742-45 (2009).

When both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony based on a particular expert's credibility is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325-26 (Fed. Cir. 2010) ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

b. Significant Aggravation

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). The United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations in *Loving*. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason

> for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this test as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *See id.* at 143; *see also Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005).

The Federal Circuit clarified *Loving* prongs 3, 4, and 5 in *Sharpe*, further defining the requirements for petitioners to successfully demonstrate a cause-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Human Servs.*, 964 F.3d 1072 (Fed. Cir. 2020). *Loving* prong three requires only a comparison of a petitioner's current, post-vaccination condition with her pre-existing pre-vaccination condition. *Id.* at 1082. A petitioner is not required to demonstrate an expected outcome or that her post-vaccination condition was worse than such an expected outcome. *Id.* at 1081.

Loving prong four requires petitioner to provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Id.* at 1083 (quoting *Loving*, 86 Fed. Cl. at 144). In other words, a petitioner is "required to present a medically plausible theory demonstrating that a vaccine 'can' cause a significant worsening" of the condition. *Id.* (citing *Pafford ex. rel. Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1356-57 (Fed. Cir. 2006)). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of his significantly aggravated injury. *Id.* (citing *Walther v. Sec'y of Health & Human Servs.*, 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alternative causation . . . once petitioner has established a prima facie case")).

Loving prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Id.* at 1085 (quoting *Loving*, 86 Fed. Cl. at 144). In other words, petitioner must show that the vaccination "did" cause a worsening of petitioner's underlying disorder. *Id.* "The sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1478; *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1377 (Fed. Cir. 2009); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). In determining causation, a special master should consider the causation opinions of the treating providers as "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect shows that the vaccination was the reason for the injury'" *Cappizano*, 440 F.3d at 1280.

IV. Discussion

Petitioner is alleging two separate injuries caused by the HPV vaccinations she received on February 18, 2013, and April 22, 2013. First, she is alleging that the HPV vaccines caused her to develop gastrointestinal injuries, such as colitis and/or gastroparesis with resultant erosive esophagitis. *See* Pet. Exs. 14, 20, &28. Then she is also alleging that the HPV vaccines caused a

significant aggravation of her pre-existing alopecia. However, the main problem with both of petitioner's claim is rooted in *Loving* Prong Five/*Althen* prong two.

a. *Loving* Prongs One-Three: Discussion and Conclusion

As summarized above, prior to receiving the HPV vaccines, petitioner had been experiencing hair-loss. *See* Pet. Ex. 2 at 84, 94-102; Pet. Ex. 4. At least on one occasion, petitioner reported to her pediatrician that her eye lashes were falling out in 2012. Pet. Ex. 9 at 5. In records that followed the administration of the HPV vaccines, she told treating doctors that her hair loss began prior to the vaccinations. When petitioner was seen by Dr. Sureyya Savasan, on December 5, 2013, petitioner reported she "noticed hair loss about one year ago," and that "[t]he hair loss mainly involves her scalp hair, eyelashes, and skin on the upper extremities." Pet. Ex. 2A at 402-03. Thus, petitioner's records establish that she had alopecia prior to the HPV vaccines administered on February 18, 2013 and April 22, 2013, satisfying *Loving* prong one.

Loving prong two requires a discussion of the petitioner's "current condition (or condition following the vaccination if that is also pertinent." *Loving,* 86 Fed. Cl. At 144. Petitioner also has demonstrated that after the vaccinations at issue, her alopecia had changed and became more widespread. At an appointment with her pediatrician on June 12, 2013, it was recorded that petitioner had a two-month history of eyebrows and eye lashes falling out. Pet. Ex. 2 at 4. While meeting with Dr. Savasan in December 2013, after the vaccinations, petitioner not only reported hair loss for one year, but that more recently she had noticed a "distinct area of hair loss on the right side of the scalp," and a "discrete area of hair loss on the left forearm which she noticed about five to six weeks ago." Pet. Ex. 2A at 403. She continued to report hair loss on different parts of her body, aside from her eyebrows and eye lashes to multiple providers and was treated accordingly. *See* Pet. Ex. 5 at 3; Pet. Ex. 24 at 2. At the time petitioner filed her responsive brief to respondent's motion, petitioner still had a diagnosis of alopecia. *See* Pet. Ex. 24 at 41.[17]

Loving prong three requires only a comparison of a petitioner's current or post-vaccination condition with her pre-vaccination condition. *Sharpe v. Sec'y of Health & Hum. Servs.* 964 Fed. Cir. 1072, 1082 (Fed. Cir. 2020); *see also Loving,* 86 Fed. Cl. at 144. The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4). As petitioner acknowledged, she had experienced some hair loss prior to vaccination and the medical records are clear that her hair loss became more widespread after receipt of the HPV vaccines, petitioner has demonstrated that there was a change in her hair loss post-vaccination. Thus, petitioner has established *Loving* prong three. However, whether the HPV vaccine was the cause of the change in petitioner's alopecia is discussed below.

b. Petitioner has not established that the HPV vaccine caused her to develop gastrointestinal injuries (colitis and/or gastroparesis with resultant erosive esophagitis) or that it significantly aggravated her pre-existing alopecia.

1. *Loving* prong four/*Althen* prong one

[17] Respondent concedes that petitioner has satisfied *Loving* prongs one and two. *See* Resp. Brief at 18, n. 17.

Under *Althen* prong one, the petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. *Andreu*, 569 F.3d at 1379; *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.

All of petitioner's experts endorsed a theory of molecular mimicry as a causal mechanism to explain how the HPV vaccine could cause an aggravation of alopecia and cause different gastrointestinal injuries. As Dr. Santoro explained succinctly in his first report, "The goal of vaccination is to induce immunity by stimulating a mild immune response, such that subsequent exposure to a pathogen, allows the body to recognize the threat and neutralize it with a more significant response, thereby minimizing deleterious effects of the microorganism." Pet. Ex. 14 at 6. When explaining molecular mimicry, he states, "There is, however, the potential that a portion of the foreign immunogen in the vaccine introduced may be structurally similar to a component of oneself. This can lead to the body creating an immune response, not just to the introduced vaccine antigen, but to normal components of oneself, thereby leading to an autoimmune reaction and disease." *Id.*

Petitioner's dermatologic expert, Dr. Glashofer also explained, "During the process of immunization, there is the potential that a portion of the foreign immunogen introduced may have a similar peptide sequence or to be structurally similar to a component of one's self. This can lead to the body creating an immune response, not just to the introduced antigen, but to normal components of one's self, thereby leading to autoimmune reactions….This theory of autoimmunity is known as molecular mimicry." Pet. Ex. 15 at 5.

Dr. Longman accepted the petitioner's experts' description of molecular mimicry, stating, "…molecular mimicry is the theoretical possibility that protein molecules from the Gardasil vaccine can mimic self-peptides that are normally produced by the body, leading to an antigen specific auto-immune response." Resp. Ex. A at 3. Dr. Santoro also endorsed an innate inflammatory response as a causal mechanism for the onset of petitioner's diarrhea, beginning roughly forty-four days after she received her second HPV vaccine. Pet. Ex. 14 at 8.

Molecular mimicry has been accepted as a sound and reliable theory to explain how vaccines, including the HPV vaccine, can result in autoimmune diseases. *See Salmins v. Sec'y of Health & Human Servs.*, No. 11-140V, 2014 WL 1569478, at *14 (Fed. Cl. Spec. Mstr. Mar. 31, 2014) (finding that the HPV vaccine can cause Guillain-Barre syndrome through a mechanism of molecular mimicry); *Harmon v. Sec'y of Health & Human Servs.,* No. 12-298V, 2017 WL 2872293, at *23 (finding that molecular mimicry is a reliable causal mechanism for how the HPV could cause a central demyelinating condition); *McCulloch v. Sec'y of Health & Human Servs.*, No. 09-293V, 2015 WL 3640610, at *28 (finding that molecular mimicry is a reliable causal mechanism for how the HPV could cause a seizure disorder). Additionally, I have also accepted that an inflammatory response to a vaccine by the innate immune system can cause vaccine-related injuries. *See Morgan v. Sec'y of Health & Hum. Servs.,* No. 13-592V, 2015 WL 9694667 (Fed. Cl. Spec. Mstr. Dec. 10, 2015) (finding that an innate inflammatory response to the Gardasil vaccine caused petitioner's ulcerative colitis). However, both theories rest on the

assumption that an individual's immune system will have an immune response, innate and adaptive, to the vaccine components. Due to the fact that petitioner has an underlying primary immune deficiency, resulting in no immune response to vaccines she has received, including the HPV vaccine, my determination as to causation turns on the analysis of *Loving* Prong Five/*Althen* Prong Two.

Due to petitioner's underlying primary immunodeficiency, the determination as to vaccine causation turns on *Loving* prong five/*Althen* prong two. As I have concluded, as will be discussed below, that she is unable to satisfy *Loving* prong five/*Althen* prong two. Therefore, it is not necessary to make a *Loving* prong four/*Althen* prong one determination. *See Winkler v. Sec'y of Health & Hum. Servs.*, No. 18-203V, 2021 WL 6276203 (Fed. Cl. Spec. Mstr. Dec. 10, 2021), *mot. for review denied,* 2022 WL 1528779, *aff'd* 88 F.4th 958 (Fed. Cir. 2023) *see also Vaughn ex rel. A.H. v. Sec'y of Health & Hum. Servs.,* 107 Fed. Cl. 212, 221-22 (2012) (finding the special master's failure to rule on *Althen* prong one was not fatal to his decision because *Althen* prong two was fatal to petitioner's claim); *Hibbard v. Sec'y of Health & Hum. Servs.,* 698 F.3d 1355, 1364 (Fed. Cir. 2012) ("Given that [petitioner] had to show both the medical plausibility of her theory of causation and that she suffered an injury consistent with that theory of causation, there was no reason to require the special master to address the first question when the answer to that question could have no possible effect on the outcome of the case.") Even if I accepted petitioner's theory *arguendo,* I find that petitioner did not provide preponderant evidence of logical sequence of cause and effect due to petitioner's pre-existing primary immunodeficiency at the time she received the two HPV vaccines in 2013, because she had no immune response to the vaccines, innate and/or adaptive.

2. *Loving* Prong Five/*Althen* Prong Two

Under *Loving* Prong Five/*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). This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Loving* at 144.*; Broekelschen,* 618 F. 3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). "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,* F.3d at 1356.

In this case, petitioner cannot show by preponderant evidence that the HPV vaccines she received in 2013 was the "but-for" cause of her gastrointestinal injuries or exacerbated her pre-existing alopecia because of her underlying primary immunodeficiency disorder.

Even though petitioner was not diagnosed with a primary immunodeficiency disease until approximately five months post-vaccination, petitioner's pre-vaccination medical history included signs and symptoms consistent with a course of a primary immunodeficiency described in the medical literature submitted in this matter, her treating physicians diagnosed petitioner with common variable immunodeficiency disease, and her medical records revealed nearly absent levels of antibodies of all classes.

The opinions of petitioner's experts were significantly flawed in two respects. First, they discounted frequent infections and hives in the year or more prior to her vaccination and made conclusory statements that petitioner was healthy prior to receiving the HPV vaccines. Second, petitioner's experts apparently relied on Dr. Marks' initial hypothesis that petitioner's extremely low immunoglobulin levels were secondary to her prolonged diarrhea while ignoring Dr. Marks' revised and ultimate opinion that petitioner had a primary immunodeficiency and because of petitioner's underlying immunodeficiency disease she had mounted no immune response to the vaccines.

Common variable immunodeficiency disease is a primary immunodeficiency disease characterized by reduced serum immunoglobulins. Resp. Ex. I at 1. Reduced levels of of IgG and IgA and/or IgM, normal or decreased B cell numbers, and impaired antibody response lead to recurrent infections, noted mostly in the respiratory and gastrointestinal tracts. Resp. Ex. D at 1; *see also* Resp. Ex. C at 1. While the underlying cause of CVID is unknown, it is described as a "failure in B cell differentiation, with impaired secretion of immunoglobulins, but T cell abnormalities, including decreased lymphocyte proliferation to mitogen and antigens, deficiency of antigen-primed T cells, and reduced production and/or expression of IL-2 and other cytokines are common." Resp. Ex. I at 1. There is a high prevalence of gastrointestinal complaints and issues among CVID patients. Resp. Ex. D at 1. According to the Khodadad article, between 20% and 60% of individuals with CVID develop diarrheal disease, and chronic watery diarrhea is common in CVID. Resp. Ex. D at 5. "Some patients with CVID present with gastrointestinal problems as their first clinical presentation, while other develop GI complications during the course of the disease." *Id.* Furthermore, while the esophagus is not commonly involved in CVID, some patients who are on chronic antibiotics can develop drug-induced esophagitis or esophageal candidiasis as a side effect of the antibiotics. *Id.*

According to the Cunningham and Rundles article, there is approximately a 4–6-year lag time between when symptoms initially occur and the diagnosis of CVID is made. Resp. Ex. I at 11. Because patients with CVID present with varied illnesses, including gastrointestinal issues or recurring respiratory infections, they are treated by multiple physicians, which can delay recognition of the antibody deficiency. *Id.* at 1. Standard treatment for CVID is periodic IVIG infusions. *Id.* at 2.

Prior to receiving the two HPV vaccinations in 2013, between January 2011 and February 2013, petitioner was treated for multiple sinus infections and given multiple courses of antibiotics for treatment. *See* Pet. Ex. 9 at 2 (January 10, 2011: diagnosed with sinusitis and prescribed Amoxicillin for ten days); Pet. Ex. 2 at 84 (May 31, 2011: Patient is status post-treatment of 21 days of Augmentin which she states alleviated her nasal congestion and pressure significantly. She also states that starting Zyrtec did not seem to significantly improve the occurrence of her hives.); Pet. Ex. 9 at 4 (December 31, 2011: 14-year old with a history of prolonged sinus infection over the spring and summer that caused hives, took an antibiotic for 3-4 weeks until it resolved); Pet. Ex. 9 at 6 (January 9, 2013: patient has painful right outer ear, also coughing and congested with yellowish sinus drainage four times a day. Diagnosed with sinusitis and was prescribed a course of Amoxicillin for ten days); Pet. Ex. 9 at 6 (January 30, 2013: patient is coughing with congestion, did not finish Amoxicillin. Diagnosed with bronchitis

and rhinitis, prescribed Azithromycin, an antibiotic); Pet. Ex. 9 at 7 (February 18, 2013: Horse voice and neck feels swollen for two days, finished Z-pack); *Id.* at 8 (April 20, 2013: patient has runny nose, coughing, and green discharge for five days. Diagnosed with bronchitis and rhinitis and gave another Z-pack); *see also* Pet. Ex. 9 at 7 (April 29, 2013: bronchitis and rhinitis sinus infection and hives all over body. Persistence of congestion and coughing. Given a course of Augmentin for fourteen days).

Despite this extensive history of chronic and recurrent sinus infections, petitioner's experts contended that petitioner did not have recurrent infections or at least that she did not have an extraordinary history of infections. Dr. Santoro wrote, "If the patient had a genetic IgG deficiency, she would have had a long history of bronchitis, pneumonia, ear infections and sinusitis, which is common with such a deficiency. *I did not see any extraordinary such reporting of these problems in [petitioner's] records.*" Pet. Ex. 20 at 3 (emphasis added). Dr. Santoro also suggested that if there had been a historical problem that pre-dated the vaccinations, petitioner would have already been treated with IVIG.

However, as explained by Dr. Longman and supported by the Cunningham-Rundles article, delay in diagnosis of CVID is common because patients present with an array of illnesses to multiple physicians. *See* Resp. Ex. G at 2; Resp. Ex. I at 1. Even though petitioner was not diagnosed with a primary immunodeficiency until September 2013, prior to her diagnosis, she was treated by multiple doctors for different issues, including urticaria, chronic sinusitis, bronchitis, warts, and prolonged diarrhea as recounted above. In 2013, petitioner had multiple trips to her primary pediatrician between January and July for chronic sinus infections with prolonged treatment with antibiotics. *See* Pet. Ex. 9 at 7-8 (4/29/13: review bronchitis and rhinitis, sinus infection; hives all over body; persistent congestion, cough, and sinus headache, a little better on antibiotics but came back; still having hives over entire body; 5/1/13: Follow-up: reaction to Augmentin? Hives all over; swollen fingers; currently on prednisone; 6/12/13: coughing, hives for three months, diarrhea for one week, refer for allergy evaluation; 6/24/13: still has diarrhea twice a day, left ear hurts, wax in both ears, urticaria resolved, prescribed Azithromycin; 7/2/13: still has diarrhea, third visit since 6/12/13, refer to GI-CHM, CBC normal).

Even with her prolonged diarrhea which began in June 2013, it was not until July 15, 2013, when allergist-immunologist Dr. James Fordyce recommended that petitioner have her antibody levels were tested. Pet. Ex. 2 at 79. On July 19, 2013, petitioner's antibody tests revealed significantly low IgA (less than 8 mg/dl), significantly low IgE (less than 2 IU/ml), low IgG serum of 70 mg/dL, and low IgM. Pet. Ex. 2 at 72. It was then petitioner was referred to Dr. Marks of immunology for the concerning low levels of antibodies.

Petitioner's treating physicians also acknowledged petitioner's history of recurrent infections when diagnosing her with a primary immunodeficiency. At petitioner's second appointment with Dr. Marks on September 25, 2013, petitioner's mother reported that petitioner had been experiencing severe warts and regular sinus infections that began two years prior. The exact note from this appointment states:

> She did call to my attention, which we did not discuss at our last visit, that [petitioner] has been experiencing quite severe plantar warts on her right foot, involving four of the five toes. In addition to this, she has been experiencing warts on her face. Again, when looking back, the warts also started approximately two years ago, which is when [petitioner] started becoming sick *quite regularly with sinus infections, per Mom.*

Pet. Ex. 2 at 56 (emphasis added). Dr. Marks opined, "Given this constellation of symptoms with complete agammaglobulinemia, recurrent infections, and warts, I do have some concerns for WHIM's syndrome; however, she does not have the typical variants with abnormalities on CBC with neutropenia that can be seen." *Id.* at 57. Additionally, when petitioner was evaluated by Dr. Brian Berman one year later, on August 27, 2014, he wrote that petitioner "was well until three years ago when she began to develop recurrent sinusitis. She received multiple antibiotics and never required hospitalization." Pet. Ex. 3 at 5. The evidence that petitioner had repeated sinus and bronchitis infections treated with antibiotics is incontrovertible and is consistent with the diagnosis of a primary immune deficiency.

Dr. Santoro also argued that petitioner's agammaglobulinemia was caused by inflammatory colitis and wrote, "Dr. Mark's opinion clearly stated that the petitioner had ulcerative colitis that this explained her low immune globulin levels after the onset of her ulcerative colitis and diarrhea, but not before," and, "[Dr. Marks] was of the opinion that [petitioner] did not have CVID." Pet. Ex. 20 at 4. While Dr. Santoro is correct that when Dr. Marks first met with petitioner on August 5, 2013, she considered that petitioner was losing "immunoglobulins of all classes through her stools," but also cautioned that she wanted to do repeat blood work after a few weeks of treatment of colitis with Asacol to see if her levels rebounded. *See* Pet. Ex. 2 at 65. When petitioner returned to Dr. Marks on September 25, 2013 and petitioner's diarrhea had subsided, she again noted that petitioner had "no immunoglobulins, including IgG, IgA, as well as IgM." *Id.* at 56. Dr. Mark's opined after this appointment "atypical agammaglobulinemia or WHIM syndrome variant." *Id.* At the November 4, 2013 follow-up with Dr. Marks, petitioner's diagnosis was "primary immune deficiency, recurrent infection, and agammaglobulinemia." Pet. Ex. 12A at 472. At petitioner's appointment with Dr. Savasan in December 2013, again she had "almost undetectable levels of immunoglobulins, including IgG, IgA, IgM, and IgE." Pet. Ex. 2A at 405. When Dr. Berman met with petitioner, he aptly diagnosed her with "B-cell immunodeficiency, with a history of presumed autoimmune alopecia and *transient inflammatory bowel process* associated with propensity toward papilloma virus," and that "the possibility of WHIM syndrome seems very real." Pet. Ex. 3 at 6. Thus, the medical records do not support Dr. Santoro's assertions that petitioner's agammaglobulinemia was secondary to her diarrhea, as her immune deficiency continued well after resolution of her diarrhea. Ultimately, Dr.Marks, Dr.Savasan and later Dr. Lauter and Dr. Berman diagnosed CVID and Dr. Marks and Savasan noted that petitioner had not mounted an immune response to the vaccines that she had received also consistent with CVID.

With respect to petitioner's alopecia, aside from her condition worsening after she received the two HPV vaccines and that alopecia areata is considered an autoimmune condition, petitioner's expert, Dr. Glashofer's opinion rested entirely on the assumption that petitioner had a reaction to the HPV vaccine. *See* Pet. Ex. 15 at 5 ("…the Gardasil vaccination set off a reaction of inducing various disease states of autoimmunity in the petitioner."). The medical

literature Dr. Glashofer referenced to support his opinion did little to advance petitioner's argument that the HPV aggravated her alopecia. The Chu et al. article is a case report of young child developing alopecia within one week of receiving a vaccine different from the HPV vaccine. Pet. Ex. 15B at 3. The Geier and Geier article is a review of VAERS data of adverse events post Gardasil vaccination, which provides evidence of increased reporting of diagnoses of alopecia post-HPV vaccination. However, even if these articles provided any mechanistic evidence which they do not, they suffer from the same problem as other general articles on the subject as applied to the present case in that it does not provide any evidence of causation in a person with a severe immune deficiency such as that suffered by the petitioner.

Petitioner also argues that Dr. Tamburro, a physician at the Cleveland Clinic, associated the Gardasil vaccine with the onset or change in petitioner's alopecia. Pet. Response at 26. This mischaracterizes the medical records from Dr. Tamburro. At petitioner's first appointment with Dr. Tamburro on July 23, 2014, Dr. Tamburro noted that petitioner's hair loss began *prior* to her diagnosis of agmmaglobulinemia in August 2013. Pet. Ex. 5 at 3. She also noted that petitioner had viral warts. *Id.* After an examination, Dr. Tamburro diagnosed petitioner with alopecia areata, verruca plana, and verruca vulgaris and wrote, "*likely related to agammaglobulinemia or other immune differential*." Pet. Ex. 5 at 4 (emphasis added). At the follow-up appointment on September 22, 2014, petitioner reported that her alopecia had worsened. *Id.* at 11. She documented multiple spots of hair loss in the frontal, parietal and occipital areas of the head as well on various other locations on her body. Dr. Tamburro diagnosed petitioner with alopecia areata and noted that it has "an unpredictable course." *Id.* at 12. Dr. Tamburro also wrote, "Alopecia areata can be triggered by vaccines (such as Gardasil), but usually would occur in closer proximity to the vaccination [than] [petitioner's] alopecia." *Id.* While Dr.Tamburro apparently answered a question about Gardasil causation of alopecia, refencing possible general vaccine causation, her opinion was that petitioner's condition was more likely related to agammaglobulinemia. This view is supported by the Cunningham-Rundles article, which notes, "For unknown reasons, autoimmune diseases, particularly autoimmune hemolytic anemia, autoimmune thrombocytopenia, rheumatoid arthritis, and pernicious anemia, are relatively common in this patient group." Resp. Ex. I at 1. Thus, the general statement of Dr. Tamburro associating alopecia causation to vaccines is not sufficient to overcome the overwhelming evidence that petitioner had a primary immunodeficiency disease that was more likely the cause of her alopecia, considering she had no response to the HPV vaccine or other vaccines she had received in the past.

Petitioner cannot show how the theories posited by her experts, which assume activation of petitioner's immune system, could cause autoimmune injuries, in the absence of an immune response to the HPV vaccine. Even if I had accepted any of petitioner's experts' theories as to vaccine causation of gastrointestinal disease or alopecia areata, there would be no logical sequence of cause and effect because petitioner did not have an immune response to the HPV vaccine, or any vaccine for that matter.

Petitioner's bloodwork included testing for antibodies against tetanus and diphtheria, which showed no antibodies to either antigen despite receiving multiple vaccines containing the two antigens. Pet. Ex. 2 at 12. At petitioner's appointment on November 3, 2013, petitioner and her mother discussed getting a flu vaccine with Dr. Marks and Dr. Marks explained, "there is no

reason that we cannot give her [a flu shot], but I do not think she will amount much of a response given her immune system at this time." Pet. Ex. 12A at 472. On the December 6, 2013 appointment record with Dr. Savasan, the "Immunization Status," section states, "[petitioner] received all of her immunizations, receiving two of the three doses of Gardasil; however, [petitioner] has not mounted an immune response to vaccines." Pet. Ex. 2 at 46; Pet. Ex. 12A at 404. These statements by Dr. Marks and Dr. Savasan are unequivocal. Not only did petitioner not have an immune response to the HPV vaccines or tetanus/diphtheria, she had repeated blood work that showed immunoglobulins were undetectable. There is no evidence that petitioner had any type of immune reaction to the HPV vaccines, either an innate or adaptive, without which it difficult to see how the vaccine could have caused a cross reaction giving rise to any of the various conditions claimed by petitioner particularly given that they were more likely explained by her CVID.

Evidence of other possible sources of injury can be relevant not only for the "factors unrelated" defense, but also as to whether prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question. *Stone v. Sec'y of Health & Hum. Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012); *see e.g. de Bazan v. Sec'y of Health & Human Servs.*, 538 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of petitioner's case-in-chief."). "In some cases, a sensible assessment of causation cannot be made while ignoring the elephant in the room—the presence of compelling evidence of a different cause for the injury in question." *Stone*, F.3d at 1380 (citing *Walther*, 485 F.3d at 1151 n.4). Here, the elephant in the room is petitioner's underlying primary immunodeficiency disease that serves as compelling evidence of a different cause of her alleged injuries, and she cannot show that the HPV vaccinations were the but-for cause of her gastrointestinal illnesses or significant aggravation of her alopecia.

For the reasons discussed above, I find that petitioner has failed to provide preponderant evidence of a local sequence of cause and effect required under *Loving* prong five/*Althen* Prong Two.

3. *Loving* Prong Six/*Althen* Prong Three

The final *Loving* prong requires petitioner to establish a "proximate temporal relationship" between the significant aggravation of his condition and the received vaccine. *Loving* 86 Fed. Cl. at 144; *see also Althen*, 418 F.3d at 1281. That term has equated to the phrase, "medically-acceptable temporal relationship." *Althen* at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* 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 also 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").

Based on petitioner's medical records, the onset of petitioner's gastrointestinal illness began in or around June 6, 2013, approximately forty-four days after she received her second HPV vaccine on April 22, 2013. Petitioner's expert, Dr. Santoro opined that this timeframe is medically appropriate for an innate inflammatory response to the vaccine and referenced *Morgan*, an HPV-ulcerative colitis case. However, aside from the fact that petitioner's underlying primary immunodeficiency disease caused her to have no immune response to the HPV vaccine, inflammatory or adaptive, the facts and expert opinion in *Morgan* differ significantly from this one. The onset of petitioner's gastrointestinal symptoms in *Morgan* began six-hours after the HPV vaccination, became continuous, she needed extensive surgical resection of her colon, and there was no alternative explanation for the onset of petitioner's symptoms. *Morgan*, 2015 WL 9694667, at *15. Further, the expert in *Morgan*, her gastrointestinal surgeon, opined that the vaccine triggered an initial innate inflammatory response and that the cytokines from the innate response signaled an adaptive immune response causing the autoimmune condition of ulcerative colitis. *Id.* In contrast, the onset of petitioner's diarrhea in this case was forty-four days after petitioner received the second HPV vaccine on April 22, 2013 and largely resolved with medication, which is more consistent with a gastrointestinal illnesses secondary to a primary immunodeficiency disease. *See* Resp. Ex. D at 5 ("Some patients may present with GI problems as their first clinical presentation, while other develop GI complications during the course of the disease."); *see also* Resp. Ex. C at 3 ("Often, in these patients, appearance of Crohn's-like inflammatory bowel disease findings in the intestine supports immunodeficiency findings that are triggered by infections of inflammatory bowel disease etiology."). Thus, the onset of petitioner's diarrhea forty-four days post-vaccination is significantly more consistent with a condition incident to common variable immune deficiency.

The date of onset of the worsening of petitioner's pre-existing alopecia is more uncertain than the date of onset of her gastrointestinal illness, aside from it happening sometime after the second HPV vaccination she received on April 22, 2013. Petitioner reported to Dr. Savasan in December 2013 that she was experiencing hair loss on her scalp and at her appointment with Dr. Berman, petitioner described developing "widespread alopecia" after she was started on IVIG infusions. *See* Pet. Ex. 12A at 403; Pet. Ex. 3 at 5. Further, one of petitioner's treating physicians, Dr. Tamburro suggested that the onset of petitioner's alopecia, or worsening of her alopecia, occurred too long after the HPV vaccination. *See* Pet. Ex. 5 at 12. The medical records would put the onset of petitioner's alopecia becoming worse approximately four to six months post-vaccination, which would exceed what has been considered an acceptable medical timeframe to infer vaccination causation. Thus, petitioner has failed to satisfy *Loving* Prong Six/*Althen* Prong Three.

V. Conclusion

After a careful review of the record, petitioner has failed to provide preponderant evidence that her gastrointestinal illness or her alopecia were caused by or were significantly aggravated by the HPV vaccines she received on February 18, 2013, and April 22, 2013. Accordingly, petitioner's claim is hereby **DISMISSED.**

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master