In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 13-529V

Filed: December 10, 2015

[TO BE PUBLISHED]

MEGAN MORGAN, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Ruling on Entitlement; Human Papillomavirus ("HPV"/"Gardasil") Vaccine; Ulcerative Colitis ("UC")

Thomas S. Reavely, Whitfield & Eddy, P.L.C., Des Moines, IA, for petitioner.
Darryl R. Wishard, United States Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Gowen, Special Master:

On July 31, 2013, Megan Morgan ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §§ 300aa-10 – 34 (2012) [2] (the "Vaccine Act" or "the Program"). Petitioner alleged that she developed ulcerative colitis ("UC") as a result of receiving a Human Papillomavirus ("HPV" or "Gardasil") vaccine on August 9, 2010. See Petition at ¶ 28.

[1] Because this published ruling contains a reasoned explanation for the action in this case, I intend to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to delete medical or other information, the disclosure of which would constitute a clearly unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

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

Petitioner has proffered both medical records and an expert medical opinion providing a theory of a causal link between her Gardasil vaccination and her injuries. Respondent has countered with an expert medical opinion. Both parties submitted medical literature.[3]

Petitioner contends that non-specific immunomodulator effects of Gardasil caused ulcerative colitis, an autoimmune disease, in petitioner, a genetically susceptible individual. Respondent contends that petitioner had manifestations of ulcerative colitis prior to vaccination in the form of lower back pain. For the reasons stated herein, I find that petitioner has provided sufficient evidence to demonstrate that Gardasil, acting as a non-specific immunomodulator, caused petitioner's UC. Accordingly, I have concluded that petitioner is entitled to compensation.

I. Procedural History

This case was filed on July 31, 2013, and assigned to then-Special Master Zane. On August 2, 2013, petitioner filed medical records detailing her diagnosis of and treatment for ulcerative colitis, as well as an expert report from Dr. John Cromwell, her gastrointestinal surgeon. See Pet. Exs. 3-5, 7, 9.

The case was reassigned to Special Master Hastings on September 5, 2013, and petitioner thereafter submitted additional medical records which included records related to her treatment for sacroiliitis in 2010. See Pet. Ex. 12. On November 13, 2013, respondent filed her Rule 4(c) report recommending against compensation under the Vaccine Act, asserting petitioner had not met the burden of proof sufficient to establish causation. Resp. Rep. at 10. Respondent also filed an expert report from Andrew S. Warner, M.D., along with the medical literature referenced therein. See Resp. Ex. A.

On January 1, 2014, the case was reassigned to Special Master Corcoran. On February 11, 2014, petitioner filed a response to respondent's Rule 4(c) report and a supplemental expert report along with medical literature from Dr. Cromwell. See Pet. Ex. 13. Respondent then filed a supplemental report along with medical literature from Dr. Warner on April 1, 2014, and additional medical literature on June 24, 2014. See Resp. Exs. H, O-P.

The case was reassigned to Special Master Gowen on September 5, 2014. Petitioner filed her pre-hearing brief on November 12, 2014, and respondent filed her pre-hearing brief on November 18, 2014. An entitlement hearing was held before the undersigned on January 13, 2015. The parties elected not to file post-hearing briefs.

II. Evidentiary Record

In 2010, prior to receiving the Gardasil vaccination at issue, petitioner saw an anesthesiologist/pain specialist, Thomas Klein, D.O., for pain in her low back and into her left hip, and was diagnosed with sacroiliitis. Pet. Ex. 11 at 2, 3. At that visit, Dr. Klein noted that

[3] I have considered the entire record in arriving at my decision (§ 300aa-13(a)(1)). This includes the medical literature submitted by both parties, which I have read and considered. I will discuss in the course of this opinion the exhibits that are more relevant to the resolution of this case.

petitioner "denie[d] any bowel or bladder problems or control issues." Id. On exam, she had "tenderness to palpation in the left sacroiliac joint area, very diffuse in the paraspinal tissue which was mild tenderness to palpation in the lumbar area." Id. at 3. Dr. Klein's report also noted that petitioner had a ruptured disc in 2006, and "she has had some vague pain ever since, but was unsure whether this was the same type of pain that she has had before." Pet. Ex. 11 at 2; Tr. at 11, 12. Likewise, in her testimony, petitioner stated that she was diagnosed with a ruptured disc in 2006, and that it was a softball-related repetitive use injury. Tr. at 12. Dr. Klein noted that an MRI "performed and read in 2007 showed a very large herniated disc at L5-S1 with some cephalad migration." Pet Ex. 11 at 3. Dr. Klein did not perform any imaging at the 2010 visit. Petitioner underwent a sacroiliac joint injection on July 19, 2010, which alleviated her pain. Tr. at 5, 17.

On August 9, 2010, petitioner received the Gardasil vaccination at an annual visit to Dr. Sheila Marean, her gynecologist. Pet. Ex. 2. at 11. That same night, petitioner began to have diarrhea and to have to use the restroom more frequently. Tr. at 19. Symptoms became worse as the week went on, and petitioner developed nausea, vomiting, headaches, bloody stools, and abdominal pain. Id.

Petitioner saw Dr. John Hines, a gastroenterologist at the Iowa Clinic, on December 2, 2010. See Pet. Ex. 3 at 32; Tr. at 21. At that appointment, she complained of diarrhea and passing blood in her stool. See Pet. Ex. 3 at 32. She was having three bowel movements per day accompanied by cramping abdominal pain, but no fever or chills. Id. She noted some nausea but no vomiting. Id. She denied any personal or family history of ulcerative colitis or Crohn's disease. Id. On exam, she had abdominal tenderness. Id. at 33.

On December 30, 2010, Dr. Hines performed a colonoscopy which showed "evidence of moderately severe ulcerative colitis affecting the transverse, descending and sigmoid colon" and extending to the rectum. Pet. Ex. 3 at 7. Biopsy showed active colitis affecting the transverse, descending, and sigmoid colon and rectum. Id. at 25. Dr. Hines started petitioner on Asacol, Mesalamine[4] enemas, and Prednisone. Id. at 7. Petitioner saw Dr. Hines for a follow up on February 2, 2011, and she reported improved symptoms since starting treatment. Pet. Ex. 3 at 20. Follow up in six months was planned. Id. at 21-22. She was instructed to continue the twice daily Mesalamine enemas until she completed the course of Prednisone, and then cut back to one enema daily along with continuing oral Asacol. Id. at 22.

On June 16, 2011, petitioner saw a physician assistant at Dr. Hines' office, reporting worsened symptoms of five to ten liquid stools daily with some blood, cramping pain, stool urgency, and a need to go to the bathroom at night. Pet. Ex. 3 at 8. She was no longer taking Prednisone, and had also discontinued Mesalamine enemas but had used them in the past two days without benefit. Id. She continued to take oral Asacol but could not increase her dosage because of heartburn with higher doses. Id. She had a reduced appetite. Id. On exam, she was tender in the abdomen. Id. at 9. The PA suggested that if her symptoms persisted despite the use of Mesalamine enemas and Asacol, she would recommend a course of Prednisone or

[4] Asacol and Mesalamine enemas are the oral and rectal forms of an active metabolite of sulfasalazine, used in the prophylaxis and treatment of inflammatory bowel disease and ulcerative colitis. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 161, 1138 (32d ed. 2012). (hereinafter, "DORLAND'S").

Azathioprine (an immunosuppressant), but noted that petitioner wished to avoid taking Prednisone if possible. Id. at 8-9. Petitioner was to follow up with Dr. Hines as scheduled in August, 2011. Id.

On July 14, 2011, petitioner went to the University of Iowa Hospitals & Clinics ("UIHC") emergency room. See Pet. Ex. 4, 1-34. She reported a history of ulcerative colitis, that she had been placed on Asacol initially with improvement, but that her symptoms had returned over the past few months. Id. at 15. That day, she reported an acute worsening of abdominal pain and the passage of blood from her rectum. Id. She had not taken Prednisone since her initial treatment by Dr. Hines. Id. at 16. On exam, she had mild abdominal tenderness. Id. at 17. She was felt to have an acute exacerbation of UC, and was given a prescription for Asacol enemas to use for five days. Id. at 18.

On August 3, 2011, petitioner saw Dr. Murad Abu Rajab, a gastroenterology fellow, and Dr. Jeremy Fields, a gastroenterologist, at UIHC for a second opinion. Pet. Ex. 4 at 47. She reported that she developed bloody diarrhea and abdominal cramping after receiving the Gardasil vaccine in August 2010. Id. Petitioner reported a 45 pound weight loss over the past four months with continued abdominal cramping, bloody diarrhea, and nocturnal symptoms. Id. Dr. Rajab recommended a repeated colonoscopy but petitioner declined. Id. at 48. Dr. Rajab thought she had not responded adequately to her current treatment and prescribed Azathioprine, and three weeks of Prednisone followed by a tapering dose. Id. Rajab discontinued Mesalamine, replacing it with sulfasalazine, another medication for ulcerative colitis. Id. Petitioner's mother called UIHC for a referral to discuss possible surgical treatments on August 9, 2011. Id. at 61.

On August 10, 2011, petitioner saw Dr. Marean for an annual exam, who noted in petitioner's record that the "group who did colonoscopy told [patient] possible from Gardasil." Pet. Ex. 2 at 9. On August 12, 2011, petitioner's mother called Dr. Hines' office to report petitioner was missing work due to stool incontinence. Pet. Ex. 3 at 11. The message indicated that petitioner had not initiated the medication changes recommended by Dr. Rajab. Id. Dr. Hines declined to complete medical leave paperwork for petitioner, noting that she had been resistant to more powerful medications, and stated that she needed to come back to the clinic for treatment. Id.

On August 17, 2011, petitioner saw Dr. Samy Maklad, a surgical resident, and Dr. John Cromwell, a gastrointestinal surgeon, from UIHC. Pet. Ex. 5 at 70-72; Pet. Ex. 4 at 64-66. She reported the onset of bloody diarrhea following the Gardasil vaccine in August 2010, with a diagnosis of ulcerative colitis in December 2010. Pet. Ex. 4 at 64. She reported that her symptoms had not been controlled with medical management, and that she continued to have eight to ten loose, bloody stools daily. Id. She reported seeing Dr. Fields for medical management of her UC, but was concerned about the side effects of the medications recommended, and wanted to explore surgical options. Id. Dr. Cromwell discussed a restorative proctocolectomy (the removal of the colon and rectum), and petitioner planned to have this surgery. Id. At a pre-operation visit with Dr. Cromwell on September 14, 2011, she reported continuing to have five to ten bloody stools daily with abdominal pain. Pet. Ex. 5 at 68. She was taking Asacol for medical management of her condition, and reported last taking Prednisone in March 2011. Id.

On November 14, 2011, petitioner underwent a laparoscopic proctocolectomy, with ileoanal J-pouch reconstruction. Pet. Ex. 4 at 878-79. She was left with an open wound. See Pet. Ex. 6 at 2, 4 at 949. She was discharged on November 26, 2011. Pet. Ex. 4 at 869. On October 31, 2012, petitioner presented to Dr. Cromwell with abdominal cramping and bloody stools, and was still having five to ten bowel movements per day. Pet. Ex. 5 at 57. Dr. Cromwell thought her diagnosis was most likely pouchitis, inflammation of the ileal pouch. Id. She was prescribed Cipro, an antibiotic, without improvements. Flagyl, another antibiotic, was added by Dr. Cromwell on November 9, 2012. Pet. Ex. 4 at 988.

At hearing, petitioner testified that she still has pain every day, has to use the restroom frequently, and still bleeds on occasion. Tr. at 24. Although she has more control now, her ulcerative colitis still affects her life—she is lucky to get three to four hours of uninterrupted sleep before having to use the restroom and uses the restroom five to ten times per day. Id.

III. Discussion

A. Legal Standards to Establish Entitlement to Compensation

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of HHS, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

In order to prevail under the Program, a petitioner must prove either a "Table" injury[5] or a causation-in-fact injury, i.e. that a vaccine listed in the Table was the cause in fact of an injury (an "off-Table" injury). Petitioner alleges she suffered an "off-Table" injury, ulcerative colitis. Therefore, petitioner must demonstrate by preponderant evidence that a covered vaccine is responsible for her injury.

An "off-Table" injury is initially established when the petitioner demonstrates by a preponderance of the evidence: (1) she received a vaccine set forth on the Vaccine Injury Table; (2) she received the vaccine in the United States; (3) she sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) the condition has persisted for more than six months. § 13(a)(1)(A). To satisfy her burden of proving causation in fact, petitioner must establish each of the three Althen factors 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 proximate temporal relationship between vaccination and injury. Althen v. Sec'y of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005); see de Bazan v. Sec'y of HHS, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); Caves v. Sec'y of HHS, 100 Fed. Cl. 119, 132 (2011), *aff. per*

[5] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

curiam, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each Althen factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See Moberly v. Sec'y of HHS, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of HHS, 931 F.2d 867, 873 (Fed. Cir. 1991).

The Federal Circuit in Althen noted that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body."* Althen, 418 F.3d at 1280 (emphasis added).

Once petitioner establishes each of the Althen factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. Knudsen v. Sec'y of HHS, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." Deribeaux v. Sec'y of HHS, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

In determining whether 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 a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu v. Sec'y of HHS, 569 F.3d 1367, 1380 (Fed. Cir. 2009) (referencing Althen, 418 F.3d 1274, Capizzano v. Sec'y of HHS, 440 F.3d 1317 (Fed. Cir. 2006)).

B. The Parties' Contentions Regarding Entitlement

There is no dispute that petitioner received a covered vaccine administered in the United States. Pet. Ex. 2 at 11. In addition, there is no dispute that petitioner suffers from ulcerative colitis and that she has undergone treatment for more than six months. Therefore, the only issue to resolve is whether the Gardasil vaccine was more likely than not the cause-in-fact of petitioner's ulcerative colitis. Petitioner presented the testimony of Dr. John Cromwell, M.D., and respondent presented the testimony of Andrew Warner, M.D.

i. Expert Credentials

1. John Cromwell, M.D.

Dr. Cromwell is board certified in general surgery and colon and rectal surgery. Tr. at 42. He is a clinical associate professor of surgery at the University of Iowa. Pet. Ex. 8 at 2. In addition, Dr. Cromwell is the director of Gastrointestinal, Minimally Invasive, and Bariatric Surgery at the University of Iowa, where he directs a group of ten surgeons who provide surgical care for all aspects of the gastrointestinal tract. Tr. at 42. He is the co-director of the James A. Clifton Center for Digestive Diseases, an outpatient facility for evaluation of patients with gastrointestinal disorders. Id. at 43. He is the medical director for an inpatient surgical unit in the hospital, and associate chief medical officer and director of surgical quality and safety for the University Hospitals. Id. In that role, he oversees the quality and safety of all the surgery that takes place at the University of Iowa from an executive standpoint. Id. Dr. Cromwell is not board-certified in gastroenterology, but works closely with and supervises the gastroenterologists at the University of Iowa. Id. at 171-72. He manages quality review of what they do, and reviews whether they have done things correctly. Id. at 172. He reviews the diagnoses of ulcerative colitis and Crohn's disease before doing surgery. Id. at 174. He is very familiar with the presentation of UC.

Dr. Cromwell has been published in a number of peer-reviewed journals. Pet. Ex. 8 at 3-4. Additionally, Dr. Cromwell has been invited to make a number of presentations to his colleagues in the field of colon and rectal surgery. Id. at 6-8. Dr. Cromwell earned his Bachelor of Science in Chemistry at Nebraska Wesleyan University. Id. at 1. He received his M.D. from the University of Minnesota Medical School, where he also completed his internship and residency in general surgery. Id.; Tr. at 44. As a resident, he worked in the transplant immunology lab at the University of Minnesota conducting research in transplant immunology. Tr. at 44. Subsequently, he completed a fellowship in Colon and Rectal Surgery at the University of Texas Health Science Center at Houston. Id. He was admitted as an expert in colon and rectal surgery without objection. Id. at 78. Dr. Cromwell was also admitted as an expert in gastroenterology over the objection of respondent, who noted that he is not board-certified in gastroenterology or internal medicine. Id. at 170-71; 173-74.

2. Andrew Warner, M.D.

Dr. Warner is a board-certified gastroenterologist, and Chairman of the Department of Gastroenterology at Lahey Clinic. Tr. at 119-20. He is also an associate clinical professor of medicine at Tufts Medical School and a clinical instructor at Harvard Medical School. Id.; Resp. Ex. B at 3. He has been Chairman of the Department of Gastroenterology at the Lahey Clinic, a Tufts Hospital, since 2000. Tr. at 120; Resp. Ex. B at 3. Dr. Warner's area of clinical specialty is the treatment of patients with Crohn's disease and ulcerative colitis. Tr. at 121.

Dr. Warner has been published in a number of peer-reviewed journals, and was previously on the editorial board of the Journal of Inflammatory Bowel Disease. Resp. Ex. B at 6; Tr. at 123. In addition, he is the author of the book *100 Questions and Answers About Crohn's disease and Ulcerative Colitis: A Lahey Clinic Guide.* Resp. Ex. B at 7; Tr. at 123-24.

Dr. Warner earned his Bachelor of Arts from Skidmore College. Resp. Ex. B at 1. He received his M.D. from Chicago Medical School. Id. Thereafter, he completed his internship and residency in internal medicine at Mt. Auburn Hospital, a Harvard Hospital, and his fellowship in gastroenterology at Lahey Clinic. Id. Dr. Warner was admitted as an expert in gastroenterology without objection. Tr. at 125.

ii. Ulcerative Colitis

Ulcerative colitis ("UC") is one of two major types of Inflammatory Bowel Disease ("IBD"), an immune-mediated chronic intestinal condition. Anthony S. Fauci et al., HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, 1886 (17th ed. 2008). With regard to the etiology of IBD,

> [a] consensus hypothesis is that in genetically predisposed individuals, both exogenous factors (e.g. normal luminal flora) and host factors (e.g. intestinal epithelial cell barrier function, innate and adaptive immune function) cause a chronic state of dysregulated mucosal immune function that is further modified by specific environmental factors . . . . Importantly, the normal intestine contains a large number of immune cells in a *chronic state of so-called physiologic inflammation*, in which the gut is poised for, but actively restrained from, full immunologic responses. During the course of infections in the normal host, full activation of the gut-associated lymphoid tissue occurs but is rapidly superseded by dampening the immune response and tissue repair. In IBD this process may not be regulated normally.
>
> Id. (emphasis added).

Current understanding of inflammatory bowel diseases like ulcerative colitis is that T-cell activation perpetuates the immune inflammatory response seen in those diseases. Id. at 1887. Inflammatory cytokines, such as IL-1, IL-6, and TNF, are noted to have diverse effects on tissues associated with IBD, including production of other inflammatory mediators and activation of the coagulation cascade in local blood vessels. Id. "These cytokines are normally produced in response to infection but are usually turned off or inhibited at the appropriate time to limit tissue damage. In IBD their activity is not regulated, resulting in an imbalance between the pro-inflammatory and anti-inflammatory mediators." Id.

Dr. Warner testified that ulcerative colitis typically starts in the rectum, and can extend throughout the entire colon. Tr. at 127. Unlike Crohn's disease, the other major type of IBD, it does not involve other parts of the gastrointestinal tract. Id. According to Dr. Warner, UC typically presents in the teenage years to early thirties, although it has been diagnosed in patients as young as five or as old as eighty-five. Id. He further testified that the typical presentation of UC involves rectal bleeding or bloody diarrhea. Id.

iii. Petitioner's Expert Testimony

Dr. Cromwell opined that non-specific immunomodulatory effects of the Gardasil vaccination could cause ulcerative colitis in susceptible individuals. Tr. at 62-63; Pet. Ex. 13 at 1. He explained that the so-called "specific response" to vaccination is the acquisition of

protection against pathogens through humoral immunity, which occurs when an antigen is delivered to the patient through an injection that stimulates the humoral immune system, and antibodies to that particular antigen are developed through a B and T helper cell mediated response. Tr. at 63, 106. But, there is also, Dr. Cromwell explained, evidence that vaccines act as "*non*-specific" immunomodulators. Id. at 63 (citing Pet. Ex. 13B at 3-4).[6] This non-specific effect occurs when a cross-reactive T memory cell is created as an effect of a vaccine, and then goes on to have non-specific effects on the body—in other words, effects that are *not* specific to the antigen that was injected for vaccination. Id. at 64, 106. Dr. Cromwell did note that to his knowledge, non-specific immunomodulatory effects have not yet been studied in Gardasil recipients but that panniculitis[7] has been reported in the literature after HPV vaccine in humans. Id. at 93, 101, 64, 89; Pet. Ex. 13 at 1-2

Current models of ulcerative colitis agree that there is both a genetic and an autoimmune component, and that some individuals with genetic risk factors are more susceptible to developing UC. Tr. at 105-06, 109; Pet. Ex. 13 at 2. Thus, Dr. Cromwell opined that "[i]t is logical that in a susceptible individual, the autoimmune component may be modulated by Gardasil to create the necessary environment to develop Ulcerative Colitis." Pet. Ex. 13 at 2; Tr. at 64. Dr. Cromwell was unable to provide a measure of petitioner's genetic susceptibility. Tr. at 93. On cross-examination, he also agreed that there is no evidence indicating any specific environmental trigger for UC, such as a particular vaccine. Id. at 94, 99 (referencing Pet. Ex. 13A).[8]

Dr. Cromwell did not believe that petitioner had evidence of ulcerative colitis prior to her Gardasil vaccination. Tr. at 60. He stated that when he performed petitioner's proctocolectomy, he did not see evidence of longstanding, severe UC in the appearance of the colon. Id. at 49-50. He disagreed with Dr. Klein's diagnosis of sacroiliitis[9] prior to petitioner's receipt of the Gardasil vaccine. Id. at 54-55, 76. Dr. Cromwell stated that sacroiliitis is diagnosed through identification of specific radiographic features, specifically, acute inflammation on MRI. Id. at 55-56, 176 (referencing Resp. Ex. J at 3).[10] He observed that the 2007 MRI, according to Dr. Klein's notes, did not show inflammation. Id. at 56-57. Rather, what the imaging did show was a large herniated disc at L5-S1, which Dr. Cromwell thought would make it very difficult to

[6] Christine S. Benn et al., *A Small Jab – A Big Effect: Nonspecific Immunomodulation by Vaccines*, 34 TRENDS IN IMMUNOLOGY (2013).

[7] Panniculitis is an inflammatory reaction of the subcutaneous adipose tissue. DORLAND'S at 1369; Tr. at 148.

[8] Bernard Khor et al., *Genetics and Pathogenesis of Inflammatory Bowel Disease*, 474 NATURE 307 (2011).

[9] Sacroiliitis is a type of arthritis which can be associated with UC, and can precede the development of bowel symptoms in UC patients. Tr. at 81-84.

[10] Lianne K.P.M. Brakenhoff et al., *The Joint-Gut Axis in Inflammatory Bowel Diseases*, 4 JOURNAL OF CROHN'S AND COLITIS 257, 259 (2010).

detect sacroiliitis of the kind associated with UC, because a herniated disc can and often does cause a radiculopathy that radiates down through the area where petitioner was complaining of pain. Id. at 57, 175. Nor did he find evidence of other types of extra-intestinal features associated with UC. Id. at 60. Dr. Cromwell also noted that sacroiliitis is very common in the absence of UC as well. Id. at 66. He emphasized that he would have ordered an MRI in July, as there was a clear history of a large L5-S1 herniated disc and a description of very diffuse pain in the paraspinal area by Dr. Klein. Id. at 175-76. The paraspinal area is not the sacroiliac joint. Id.

Dr. Cromwell explained that after receiving a vaccination, there is a cytokine cascade that can cause fever and illness, including diarrhea, and that the timing of the onset of petitioner's symptoms, about six hours after vaccination, was in keeping with a cytokine response causing diarrhea. Tr. at 107. It was his opinion that this cytokine cascade could potentially activate the non-specific immunomodulatory effect of the vaccine. Id. at 67, 107. He explained that the onset of ulcerative colitis is an inflammatory reaction at the outset—there is inflammation in the innermost lining of the colon. Id. at 105-6. He proposed that the non-specific effects of vaccines due to cross reactivity to T-cells involve both an inflammatory and immune response, and in a susceptible individual, the initial inflammatory process then could have "turned into a pathological immune response through the cytokine-related mechanisms." Id. at 117. In turn, he noted that the literature supports the fact that the non-specific effects of vaccines appear to be maximal in the first six months after immunization, and Dr. Cromwell noted that it was within this time frame following Gardasil administration that petitioner was diagnosed with UC. Id. at 67, 91; Pet. Ex. 13 at 2 (citing Pet. Ex. 13C at 1).[11] In other words, Dr. Cromwell's theory is that petitioner had a cytokine response that caused diarrhea within six hours after vaccination, which developed into full blown UC about a week later through the non-specific, adaptive immune response, within the time frame where he would expect a non-specific cross reactive immune response. Tr. at 107, 112, 114.

iv. Respondent's Expert Testimony

Dr. Warner's opinion was that the Gardasil vaccine did not cause or contribute to petitioner's ulcerative colitis. Tr. at 130-31. He stated that the etiology of UC is unknown and there is nothing in the literature that Dr. Cromwell submitted that supports his theory of causation or that the Gardasil vaccine in particular can cause or contribute to UC. See id. at 128-36. Dr. Warner pointed out that he had not seen an uptick in UC cases post-Gardasil. Id. at 161-62. He cited medical literature in support of the contention that vaccines, and the HPV vaccine in particular, are considered safe in patients with UC, although Dr. Cromwell correctly noted that the issue in petitioner's case is whether Gardasil can trigger the *development* of UC, not whether

[11] Frank Shann, *The Non-Specific Effects of Vaccines*, 95 DISEASE IN CHILDHOOD 662, 662 (2009).

it is safe to use in patients who already have UC. Tr. at 136-38, 70 (referencing Resp. Exs. C,[12] D,[13] E[14]).

Dr. Warner agreed with Dr. Klein that petitioner had left sacroiliitis prior to vaccination in 2010, and based on the sacroiliitis diagnosis, it was his opinion that petitioner had ulcerative colitis prior to her vaccination on August 9, 2010. Tr. at 139-40. Dr. Warner explained that UC can have manifestations outside the colon, that arthritis is the most common of these, occurring in twenty to thirty percent of UC patients, and that arthritis can occur two to three years before the UC diagnosis. Id. at 141, 144. He stated that it is not necessary to do an imaging study to make a diagnosis of sacroiliitis. Id. at 140-41, 159 (referencing Resp. Ex. J at 5).[15] Dr. Warner agreed with Dr. Cromwell that the imaging study done in 2007 showed a herniated disc, not sacroiliitis. Id. at 142. However, Dr. Warner opined that the fact that the imaging study did not show sacroiliitis in 2007 indicated that the trauma petitioner suffered playing softball in college, prior to the 2007 imaging study, was not the source of her sacroiliitis. Id. at 142. Dr. Warner noted that although she had low-grade achiness between 2006 and 2010, she went years without seeing a doctor for her lower back, which suggests the trauma was not an ongoing problem. Id. at 143, 151. However, he acknowledged that no MRI was done in 2010, and he was relying on the MRI from 2007. Id. at 153-54. He also agreed that it is fairly common that symptoms from lower back discs wax and wane over the years with pain symptoms resulting from a disc periodically becoming inflamed and putting pressure on a nerve root. Id. at 164. He testified that the diagnosis of sacroiliitis can be made by palpation of the sacroiliac joint, which would involve pushing on the person's buttock and not on the lumbar spine. Id. at 165.

Assuming that a vaccine could cause ulcerative colitis, Dr. Warner agreed that six months was a reasonable time frame in which it would do so. Tr. at 146-47. He stated that usually patients with UC are the only one in their family who has it, and genetic testing is typically not done. There was nothing unusual about petitioner that would suggest a lack of genetic susceptibility. Id. at 160-61.

C. Analysis

The questions presented by all three prongs of Althen are at issue in this case. First, could the Gardasil vaccine cause ulcerative colitis in a susceptible individual through non-specific immunomodulatory effects? Second, has the petitioner presented a logical cause and

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[12] Bruce E. Sands, MD, MS et al., *Guidelines for Immunizations in Patients with Inflammatory Bowel Disease*, 10 INFLAMMATORY BOWEL DISEASE 677 (2004).

[13] Gil Y. Melmed, MD, MS, *Vaccination Strategies for Patients with Inflammatory Bowel Disease on Immunomodulators and Biologics*, 15 INFLAMMATORY BOWEL DISEASE 1410 (2009).

[14] Denise L. Jacobson, PhD, MPH, et al., *Immunogenicity and Tolerability to Human Papillomavirus-Like Particle Vaccine in Girls and Young Women with Inflammatory Bowel Disease*, 19 INFLAMMATORY BOWEL DISEASE 1441 (2013).

[15] Brakenhoff, *supra* note 10 at 261.

effect explanation for how it did so? Third, was there a proximate temporal relationship between the vaccination and injury?

i. Althen Prong One

In this case, Ms. Morgan testified that she initially experienced three bouts of diarrhea about six hours after she received the Gardasil vaccine, on August 9, 2010. Tr. at 19. During the following week, she experienced diarrhea, nausea, vomiting, headaches, and by the end of the week, bloody stools. Id. She saw the gastroenterologist, Dr. Hines, at the Iowa Clinic on December 2, 2010, and he noted a history of uncontrollable diarrhea for three months, passing blood for six weeks, three bowel movements per day with cramping and pain in the left side of her abdomen. Pet. Ex. 3 at 32. He confirmed ulcerative colitis with a colonoscopy. Id. at 7.

Althen, prong one requires petitioner to set forth a medical theory explaining how the received vaccine could have caused the alleged injury. Althen, 418 F.3d at 1278. Both Dr. Cromwell and Dr. Warner agree that Ms. Morgan has ulcerative colitis and agree that UC is an autoimmune disease. Both also agree that the cause of UC is not well understood and much is not known about the function of the immune system in the human intestines.

Dr. Cromwell theorized that the cytokine cascade generated rapidly by the innate immune system, which can cause fever and illness, can also cause the initial symptoms of diarrhea. It also triggers the adaptive immune system, in particular the T-cell response, causing the ultimate onset of bloody stools and ulcerative colitis. Tr. at 67-68, 111-12. Dr. Cromwell explained that mechanically, when UC occurs, there is initially an inflammatory response in the innermost or mucosal lining of the colon. Id. at 105. The inflammation causes a secretory response, which causes a sloughing off of the lining of the colon and the bowel. Id. He explained that once the process begins, in patients who go on to develop UC, the patient develops a cytotoxic environment which causes a vicious cycle of more inflammatory response until the patient is put on immune suppression. Id. at 113. He attributed the relationship between the vaccine and the initiation of the inflammatory bowel disease ("IBD") to the triggering of a non-specific autoimmune response in a susceptible individual. Id. at 62-64.

Dr. Cromwell submitted an article by Bernard Khor et al., which presented a detailed review of the knowledge of causal factors in the etiology of inflammatory bowel disease. Pet. Ex. 13A.[16] The article noted that non-genetic factors may have an even more important role in ulcerative colitis than in Crohn's disease, and that both the innate and adaptive immune systems were crucial for intestinal homeostasis. Id. at 1. In particular, the article explained:

> Intestinal homeostasis involves the coordinated actions of epithelial, innate and adaptive immune cells. Barrier permeability permits microbial incursion, which is detected by the innate immune system, which then orchestrates appropriate tolerogenic, inflammatory and restitutive responses in part by releasing extracellular mediators that recruit other cellular components, including adaptive immune cells. Genetic variants, the microbiota and immune factors affect the balance of these signals.

[16] Khor, *supra* note 8.

Id. at 3. The article further discussed the role of pro-inflammatory cytokines, macrophages, and dendritic cells as crucial players in the tolerance of commensal bacteria in the intestinal lumen, which promote digestion, and the response to pathogens that breach the mucosal barrier stimulating an inflammatory response. The authors noted "[i]mmune stimulatory effects of the microbiota are important to promote an effective response against potential pathogens, although dysregulated interactions, which might arise from perturbations in host, microbial or environmental factors, could lead to a loss of tolerance and promote intestinal inflammation." Id. at 9. "Viral infections are common, and key studies highlight their potential to exert important immune modulatory effects. Acute and/or chronic viral infections could interact with host-susceptibility factors in a manner that leaves either the cell or the cellular milieu poised to promote pathological intestinal inflammation after subsequent triggering events." Id. Ultimately, the article concluded that more research is needed to more fully understand the effects of exogenous or environmental factors in promoting inflammatory bowel disease, but does discuss the important role of both the innate and adaptive immune systems in causing inflammatory bowel disease. See generally, id.; Tr. at 99.

Dr. Cromwell also referenced articles in the medical literature that discussed the non-specific effects of vaccines. See Pet. Exs. 13B,[17] 13C.[18] The articles discussed both the unintended immunities to diseases or antigens not in the vaccine as well as unintended autoimmune responses. Dr. Cromwell cited the Benn article for the explanation that T-cells are the most likely immunomodulators causing non-specific autoimmune responses. Tr. at 62-63 (referencing Pet. Ex. 13B). In particular, he referenced the portion of the article that said: "In other scenarios detrimental heterologous (non-specific) immunity can lead to severe immunopathology." Pet. Ex. 13B at 4. The article discussed lymphocytic choriomeningitis virus (LCMV)-immune mice developing severe panniculitis in the form of inflammation and necrosis of visceral fat tissue. Id. Dr. Cromwell noted that the article observed that subcutaneous fat pathology, erythema nodosum, has been seen in humans after vaccination with vaccinia virus, human papilloma virus, and hepatitis B virus. Tr. at 64, 89-90; Pet. Ex. 13B at 4. He acknowledged that these references do not create direct proof, but do show a logical sequence of events to explain why a susceptible individual could get a chronic inflammatory condition from a vaccination. Tr. at 64. He testified that the cause of ulcerative colitis is usually unknown but, in the circumstances of this case, the Gardasil vaccine was more likely than not the cause of the UC, and without it Ms. Morgan would not have developed the disease. Id. at 104.

In support of his opinion, Dr. Cromwell also pointed to several other reports of ulcerative colitis after Gardasil vaccines in the VAERS database, and opined that the incidence of adverse events after vaccines is likely substantially underreported in the VAERS database. Tr. at 72-73, 100.

Dr. Warner, on the other hand, testified that there was not sufficient evidence to connect the vaccine to ulcerative colitis. He said that he "stick[s] with the party line" that we don't know what causes UC. Tr. at 167. He testified that it is common for people who develop a devastating

[17] Benn, *supra* note 6.

[18] Shann, *supra* note 11.

disease, as Ms. Morgan had, to search for explanations and attribute a cause to something that had occurred in their lives. Id. He stated that there is nothing in the literature that connects Gardasil or HPV to UC, and discounted the articles submitted by the petitioner regarding non-specific effects of vaccines as not containing specific references to Gardasil and essentially just being general discussions of unintended events. Id. at 134-35, 132-36. He submitted two articles that discussed adverse events after Gardasil, which did not mention inflammatory bowel disease as one of the events, and several articles that reviewed the immunogenicity of vaccines in patients with inflammatory bowel disease and the safety of immunizing patients with IBD. See generally, Resp. Exs. C,[19] D,[20] E,[21] F,[22] G.[23] These articles did not identify significant elevated risk in vaccinating patients with inflammatory bowel disease. Dr. Warner stated that he has not seen an uptick in ulcerative colitis in his practice in eastern Massachusetts, which he would expect if there was a connection as most young people there are vaccinated with Gardasil. Tr. at 161-62. While he acknowledged that he was not an immunologist and did not understand all of the details in the Khor article submitted by petitioner, he criticized the article as being a "review," and for discussing "non-specific" immune-mediated responses in inflammatory bowel disease, which he contended is without meaning. Id. at 132-33 (referencing Pet. Ex. 13A).

In this case, neither expert was an immunologist, but both were quite familiar with the diagnosis and treatment of ulcerative colitis. Dr. Warner, as a practicing gastroenterologist, and Chairman of the Department of Gastroenterology at the Lahey Clinic in Massachusetts, sees numerous patients with UC or Crohn's Disease. Tr. at 119-21. Dr. Cromwell, as the director of Gastrointestinal, Minimally Invasive, and Bariatric Surgery at the University of Iowa, co-director of the James A. Clifton Center for Digestive Diseases, and associate chief medical officer and director of surgical quality and safety for the University of Iowa Hospitals also regularly sees and treats these diseases. Id. at 42-43. In this case, Dr. Cromwell also had the advantage of being Ms. Morgan's treating surgeon, who saw her during the course of the disease, performed extensive surgery, and followed her afterwards. Id. at 49-51. Dr. Cromwell concluded that she was most likely a susceptible individual whose immune system was triggered by the vaccine to cause the inflammatory response in her colon. Id. at 117. He provided medical research regarding the theoretical basis for the non-specific immunomodulatory role of exogenous factors combining with the genetic susceptibility of the patient to cause the onset of inflammatory bowel disease. He explained, in general, the role of the innate immune system in generating an early cytokine response causing Ms. Morgan's early diarrhea, which then evolved into a likely T-cell mediated UC over the course of about a week. In addition, he considered alternative

[19] Sands, *supra* note 12.

[20] Melmed, *supra* note 13.

[21] Jacobson, *supra* note 14.

[22] Barbara A. Slade et al., *Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine*, 302 JAMA 750 (2009).

[23] Julianne Gee et al., *Monitoring the Safety of Quadrivalent Human Papillomavirus Vaccine: Findings from the Vaccine Safety Datalink*, 29 VACCINE 8279 (2011).

explanations and concluded that there were none as likely as the one he proposed. Id. at 69. He was significantly persuaded by the proximity of the onset of the disease to the vaccination in a previously healthy young woman. Id. at 68-69. He provided literature references that discussed autoimmune responses to vaccines. Both doctors agreed that UC is an autoimmune disease. Id. at 109, 155.

At the theoretical level, Dr. Warner essentially testified that the cause of ulcerative colitis is unknown, and that literature references were not specific as to the cause of inflammatory bowel disease or to Gardasil being a cause. He concluded that the onset of the disease shortly after the vaccine, assuming that is when it occurred, was a coincidence.

As noted above, the Federal Circuit in Althen held that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body."* Althen, 418 F.3d at 1280 (emphasis added). A claimant thus may be entitled to recover even though her theory about the link between the vaccine and her intestinal disease "involve[s] a sequence hitherto unproven in medicine." A petitioner can satisfy Althen prong one without producing medical literature, epidemiological studies, or offering a theory that has general acceptance in the medical or scientific communities. Andreu, 569 F.3d at 1378-79 (citing Capizzano, 440 F 3d. at 1325-26). The proof need not rise to the level of scientific certainty, but rather to the Vaccine Act's preponderance standard under the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants. Capizzano, 440 F.3d at 1325-26. The Federal Circuit has held that "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Id. at 1326.

While both doctors recognized that the scientific and medical understanding of the cause of ulcerative colitis is not well understood, Dr. Cromwell presented a reasonable theory invoking the role of both the initial innate response to the vaccine antigen and of the adaptive "non-specific" response. His theory reasonably comported with the potential theories of inflammatory bowel disease causation discussed in the Khor article, and with the notion of non-specific or unintended responses to vaccines discussed in the Benn and Shann articles. I am persuaded that he provided a reasonable scientific explanation of causation given the current state of medical knowledge.

ii. Althen Prong Two

Althen, prong two requires the showing of a logical explanation for how the vaccine caused the injury. The Federal Circuit has held that "a logical sequence of cause and effect means what it sounds like—the claimant's theory of cause and effect must be logical." Capizzano, 440 F.3d at 1326.

Ms. Morgan testified that she had been an intercollegiate softball player and suffered what was described as a large herniated disc at L5-S1 in 2006. Tr. at 11-12. This was

demonstrated by an MRI in 2007, which did not show sacroiliitis. Id. at 154-155, 177-78. Ms. Morgan testified that she had two epidurals in 2007 to treat the disc pain, and that in the interim before seeing Dr. Klein, an anesthesiologist/pain management doctor, in 2010, she had a dull ache in the lower back but nothing that required treatment. Id. at 16, 31. She had stopped playing softball, so was no longer putting the same kind of stress on her low back. Id. at 31. She further testified that the pain in her back in 2010 felt similar to before—it was in the same location and although it stretched down a little bit further, was the same feeling, but not quite as intense. Id. at 30. She did not have an MRI in July of 2010, when Dr. Klein injected her sacroiliac joint. Tr. at 5, 17.

Dr. Warner focused on the issue of Ms. Morgan's low back pain as the first manifestation of ulcerative colitis. He said that although we tend to think of UC as only involving the colon, there are extra-colonic manifestations, the most common of which is arthritis, which he believes would appear in thirty to sixty percent of patients if they were tested for it. Tr. at 130. Dr. Warner concluded after review of the records that the low back pain for which Ms. Morgan saw an anesthesiologist on July 15, 2010, about three weeks before the vaccination and onset of the gastrointestinal symptoms, was actually the initial manifestation of UC and not pain emanating from the L5-S1 nerve root where she previously had a documented herniated disc. Id. at 139-43. Accordingly, he opined that she was already suffering from UC in the month before the vaccination even though she had no bowel symptoms. Id. at 140.

Dr. Warner attached significance to the fact that Ms. Morgan did not have sufficient back pain to seek treatment after the initial treatment in 2007 until she went to an anesthesiologist, Dr. Klein, in July 2010. Tr. at 143. He also argued that Dr. Klein diagnosed sacroiliitis, not lumbar disc disease, and treated the symptoms accordingly with an injection into the sacroiliac joint. Id. at 139-40. He noted that Dr. Klein made this diagnosis by pressing or palpating near the spine and then near the joint. Dr. Warner said that if the pain was not near the spine but on the joint, then a doctor could diagnose sacroiliitis. Id. at 165-66.

Dr. Cromwell agreed that he would perform the same physical examination that Dr. Warner suggested and Dr. Klein performed, however, he testified that the diagnosis of sacroiliitis is made by imaging, particularly when there is a history of a significant herniated disc at L5-S1, which could readily explain the presence of low back pain in the area of the sacroiliac joint. Tr. at 175-76. Dr. Warner pointed to the thorough physical exam and diagnosis done by Dr. Klein, but Dr. Cromwell observed that the description Dr. Klein recorded in his chart was not nearly so clear. Id. at 139-40, 175-76. Dr. Klein's note of his physical exam stated: "Palpation: Positive for tenderness to palpation in the left sacroiliac joint area, very diffuse in the paraspinal tissue which was mild tenderness to palpation in the lumbar area." Pet. Ex. 11 at 3; Tr. at 175-76. Dr. Cromwell testified that paraspinal pain is not sacroiliac pain. He said that while he would have done the same physical exam in the office, he would have also ordered an MRI, as he did not believe that a diagnosis of sacroiliitis could be made in light of Ms. Morgan's history of a large herniated disc at L5-S1 that can cause a radiculopathy that radiates down through the area where she was complaining of pain. Tr. at 175-76.

Dr. Warner submitted several articles to explain the connection between arthritic symptoms and inflammatory bowel disease. See Resp. Exs. J-P. The Brakenhoff article

indicated that extra-intestinal symptoms of IBD occur in six to thirty-six percent of cases. Resp. Ex. J[24] at 2. The article stated that peripheral and axial arthropathies are common, and isolated sacroiliitis occurs in two to thirty-two percent of cases. Id. at 3. Consistent with Dr. Warner's testimony, the authors noted "[t]he onset [of peripheral arthritis] may precede the onset of bowel symptoms although it usually coincides with or presents after the onset of IBD." Id. However, inconsistently with Dr. Warner's testimony, Brakenhoff distinguished isolated sacroiliitis, which Ms. Morgan had, from peripheral arthritis and wrote:

> Isolated sacroiliitis is an inflammation of the sacroiliac (SI) joints, consisting of uni- or bilaterally inflammation, which is mostly asymptomatic. Symptomatic patients may present with pain in the pelvis and/or decreased spinal mobility. *Sacroiliitis is diagnosed by imaging methods such as conventional radiographs and CT showing sclerosis, erosions and/or ankylosis, or by MRI showing acute inflammation* with or without structural changes.

Id. The article further noted that the diagnosis of peripheral arthritis is one of exclusion, based on the exclusion of other forms of arthritis. Id. The other articles submitted by respondent consistently reported that sacroiliitis does occur in conjunction with inflammatory bowel disease, with the numbers varying within the range described in Brakenhoff. See, e.g., Resp. Ex. P[25] at 4; Resp. Ex. O[26] at 3. Most of the articles described symptoms occurring in conjunction with the bowel symptoms, but also recognized that the joint symptoms sometimes occured first. See, e.g., Resp. Ex. N[27] at 3. In all instances, the diagnosis of sacroiliitis was made by either CT or MRI imaging. See Resp. Ex. J-P.

Dr. Cromwell agreed that ulcerative colitis can have extra-colonic manifestations, including sacroiliitis. However, he did not think that Ms. Morgan had extra-colonic symptoms of sacroiliitis in July of 2010, as radicular pain from a well diagnosed herniated disc at L5-S1 would be a more common and likely explanation for the pain that Ms. Morgan described. Tr. at 57-58. Dr. Klein's note was unclear as to the site of the pain and was consistent with radicular pain from the disc as well as sacroiliitis even though he did inject the disc. Id. at 76. In addition, as Ms. Morgan's treating gastrointestinal surgeon at the University of Iowa, Dr. Cromwell removed her bowel and large intestine and fashioned a new rectum, called a J-pouch, by attaching the small intestine to the anal canal. Pet. Ex. 4 at 878-79; Tr. at 51. He observed the condition of the bowel at surgery, and testified that it did not have the appearance of a bowel with long standing ulcerative colitis, and was therefore consistent with the post-vaccination onset. Tr. at 49. He also followed Ms. Morgan post-surgically. Id. at 51.

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[24] Brakenhoff, *supra* note 10 at 258.

[25] N. McEniff et al., *Asymptomatic Sacroiliitis in Inflammatory Bowel Disease*, 19 CLINICAL IMAGING 258, 261 (1995).

[26] R. Queiro et al., *Subclinical Sacroiliitis in Inflammatory Bowel Disease: A Clinical and Follow-up Study*, 19 CLINICAL RHEUMATOLOGY 445, 447 (2000).

[27] Chang-Hee Suh et al., *Arthritic Manifestations of Inflammatory Bowel Disease*, 13 J. Korean Med. Sci. 39, 41 (1998).

He testified that the timing of the onset of Ms. Morgan's symptoms provided "extraordinarily compelling" support for causation. Tr. at 68. He said that for a person to have gone through her entire life with no symptoms of bowel inflammation and then to experience life changing alteration in bowel habits within hours to days after receiving a vaccination is very compelling. Id. In addition, he said that the proximate transition to ulcerative colitis so closely associated with the vaccine, particularly given the logical scientific support for non-specific pathologic effects of vaccines in animal studies, is too coincidental to be caused by chance. Id. at 71-72. He opined that it was more likely than not that the Gardasil vaccine triggered the onset of the UC, and that there was no plausible alternative explanation. Id. at 69, 103-4.

The literature submitted by Dr. Warner suggests that extra-colonic symptoms *can* occur before bowel symptoms in ulcerative colitis, but most often they occur in conjunction with the colonic manifestations. Dr. Warner agreed that it is common for symptoms of a herniated disc to wax and wane, and for people to periodically become symptomatic from a prior ruptured disc because of inflammation and pressure on a nerve root. Tr. at 164. It is well known that dermatomal pain from the L5-S1 nerve root can and frequently does run through the area of the sacroiliac joint. Id. at 57-58. I am persuaded that the diagnosis of extra-colonic sacroiliitis could not be competently made in the case of a young woman with an undisputed history of a large herniated lumbar disc without having an MRI. Given Ms. Morgan's history as documented by the prior MRI, her history of mild ongoing pain that was becoming worse in the same area, and the general description of the area of pain given by Dr. Klein, the evidence suggests that radicular pain from the L5-S1 nerve root is the more likely explanation for the pre-vaccine back pain.

As explained above, Dr. Cromwell's theory that an early cytokine response initially caused diarrhea, and a later T-cell mediated response caused bloody stools and full blown ulcerative colitis, is logical even if it is a sequence "hitherto unproven in medicine." Althen, 418 F.3d at 1280. He considered and ruled out alternative explanations and found the timing "extraordinarily compelling." Tr. at 68-69. Accordingly, Dr. Cromwell's explanation is logical and more likely than not given the present state of medical knowledge.

iii. Althen Prong Three

Dr. Cromwell found the timing to be extraordinarily compelling in this case. He stated that the manifestation of ulcerative colitis was most unlikely to be explained by sheer chance when a young woman who had never experienced any bowel symptoms before developed full blown UC within about a week of receiving the vaccine. Tr. at 68. Dr. Warner testified that he thought symptom onset six hours post-vaccination would be a "little quick" for a T-cell mediated reaction, but noted that he was not an immunologist. Id. at 147. He did agree that the six-month time frame for the onset of non-specific reactions to a vaccine, for which Dr. Cromwell cited the Shann article, would be reasonable. Id.

Dr. Cromwell did not opine that the T-cell mediated response occurred within six hours. Tr. at 107. Rather, he testified that an innate, cytokine response, triggered by the vaccine, likely occurred on the evening of the vaccination causing the initial inflammation and secretory

response in the form of diarrhea. Id. at 107-08, 114. Consistent with the discussion of the coordinated immune response in the bowel in the Khor article, Dr. Cromwell testified that cytokine signaling from the innate response likely generated a non-specific, adaptive response in the already inflamed and irritated bowel. Id. at 105-108, 114. The non-specific, adaptive response occurred within about a week, when petitioner began to have bloody bowel movements, the hallmark of ulcerative colitis. Id. Dr. Cromwell opined that the one week time frame is consistent with the medical literature on non-specific adaptive immune response. Id.

As noted above, Dr. Cromwell explained that when ulcerative colitis occurs, there is an initial inflammatory response, which causes a secretory response and sloughing of the lining of the colon (i.e. diarrhea). Tr. at 105. He explained that after receiving a vaccination, there is a cytokine cascade that can cause fever and illness, including diarrhea. Id. at 107. In most individuals, a cytokine response to vaccination would be self-limiting, and would not progress into full-blown UC. Id. at 115. However, in a susceptible individual, the inflammation caused by the cytokine response could signal a coordinated response from the adaptive immune system, and bring about a T-cell mediated immune response, causing UC. A T-cell mediated response would not occur within the time frame petitioner experienced diarrhea post-vaccination. Id. at 147. However, in this case, Dr. Cromwell's cytokine theory provided a persuasive explanation, consistent with the current understanding of immunology, that petitioner's initial inflammatory response on the evening of vaccination was caused by an innate immune response, which occurs fairly quickly after a vaccination. The innate immune response caused inflammation in petitioner's colon, which caused her diarrhea. The cytokines triggered by the innate immune response also signaled a coordinated adaptive immune response, causing the autoimmune condition, UC. Thus, petitioner's diarrhea, originally caused by the innate immune response, failed to resolve, and progressed to UC as a result of the later adaptive immune response, which was part of the continuum triggered by the vaccine. Id. at 114. This progression occurred about a week later, as evidenced by the onset of bloody stools, which is within the time frame medically expected for a T-cell mediated response. Id. Accordingly, I have concluded that the timing as explained by Dr. Cromwell is reasonable and consistent with the theory that he has proposed.

IV. Conclusion

In this, as in many cases in this Program, the Althen prongs are addressed by circumstantial evidence, and based on a theoretical construct that is consistent with at least general knowledge of the immune system. In this case, neither expert was an immunologist, but it was not lost upon the court that the Director of Gastrointestinal, Minimally Invasive, and Bariatric Surgery at the University of Iowa felt sufficiently strongly about the causal connection in his patient's case to prepare the research and spend an entire day at a hearing to explain her case. As noted in Capizzano and Andreu, the testimony of treating physicians can be quite probative, 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.'" Capizzano, 440 F.3d at 1326; Andreu, 569 F.3d at 1375. A treating physician may rely on the close temporal proximity between a vaccine and an injury in concluding that there is a logical sequence of cause and effect between the vaccine and the injury. Capizzano, at 1326. In this case, Dr. Cromwell found the timing of the onset of ulcerative colitis to be extraordinarily

compelling, and he could find no reasonable alternative explanation. He had the opportunity to view the evolution of the disease and the bowel itself at surgery, and drew upon his immunology training from a transplant residency to develop a reasonable theory to explain how the vaccine could and did trigger the disease in Ms. Morgan. Accordingly, I have concluded that petitioner is entitled to compensation.

IT IS SO ORDERED.

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