In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

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ADAM GAPEN,	*	
	*	No. 19-422V
Petitioner,	*	Special Master Christian J.
	*	Moran
	*	
v.	*	Filed: May 5, 2022
	*	
SECRETARY OF HEALTH	*	Pneumococcal conjugate PCV-13 vaccine; serum sickness
	*	like reaction ("SSLR");
AND HUMAN SERVICES,	*	significant aggravation;
	*	ulcerative colitis ("UC")
Respondent.	*	
* *		

Kathleen M. Loucks, Lommen Abdo Law Firm, Minneapolis, MN, for petitioner.
Lynn C. Schlie, United States Dep't of Justice, Washington, D.C., for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

On March 21, 2019, Adam Gapen ("petitioner") filed a petition for compensation. Mr. Gapen alleges the pneumococcal conjugate ("Prevnar" or "PCV-13") vaccine he received on May 24, 2016 caused him to develop a serum sickness like reaction ("SSLR") and a significant aggravation of his underlying ulcerative colitis ("UC").[2] Am. Pet., filed May 4, 2020, at 1.

[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website. This posting will make the decision available to anyone with the internet. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

[2] The initial petition alleged the PCV-13 vaccine caused erythema multiforme ("EM") or Stevens-Johnson syndrome ("SJS"). The amended petition claims the vaccine caused an SSLR, significantly aggravating Mr. Gapen's UC. Thus, Mr. Gapen is not pursuing a causation-in-fact

After carefully weighing and assessing the evidence presented in this case, the undersigned finds Mr. Gapen has not met his legal burden. Preponderant evidence does not support the finding that the PCV-13 vaccine Mr. Gapen received significantly aggravated his UC. Accordingly, Mr. Gapen is not entitled to compensation.

I. Legal Standard

In the Vaccine Program, a petitioner is entitled to compensation if the special master determines, "on the record as a whole," that petitioner has "demonstrated by a preponderance of the evidence the matters required in the petition by [§ 300aa-11(c)(1)], and that there is not a preponderance of evidence that the illness, disability, [etc.] described in the petition is due to factors unrelated to the [vaccination]." 42 U.S.C. § 300aa-13(a)(1)(A)–(B). Compensation cannot be awarded "based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion." 42 U.S.C. § 300aa-13(a)(1). Although not binding, the special master must consider all "diagos[e]s, conclusion[s], [and] medical judgment[s] . . . regarding the nature, causation, and aggravation of the petitioner's [condition]," as well as evaluative and diagnostic tests. 42 U.S.C. § 300aa-13(b)(1). Special masters must "consider the entire record and the course of" the petitioner's condition. Id.

To receive compensation under the Vaccine Act, the petitioner must demonstrate either that: (1) his condition is a "Table Injury," and it resulted from the receipt of a covered vaccine or vaccines within the time frame set forth by the Vaccine Injury Table; or (2) his condition is an "off-Table Injury," one not listed on the Table, that resulted from his receipt of a covered vaccine. See 42 U.S.C. § 300aa-11(c)(1)(C); Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1321 (Fed. Cir. 2010); Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Mr. Gapen's claim that the PCV-13 vaccine significantly aggravated his ulcerative colitis does not fall within the Vaccine table. Thus, Mr. Gapen must prove that the Prevnar vaccination was the cause-in-fact of the aggravation of his condition. 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." 42 U.S.C. § 300aa-33(4).

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claim. In other words, his claim is not simply that the PCV-13 vaccine caused an SSLR. Rather, the development of an SSLR is only a step for his significant aggravation claim.

In Althen v. Sec'y of Health & Hum. Servs., the Federal Circuit articulated a three-prong test to assess whether a petitioner has demonstrated a causal link between a vaccine and the claimed injury. 418 F.3d 1274, 1278 (Fed. Cir. 2005). The evidentiary burden is expanded for substantial aggravation claims, adding additional considerations to the Althen prongs. See Loving v. Sec'y of Health and Hum. Servs., 86 Fed. Cl. 135, 144 (2009). The six factors required to establish a significant aggravation showing include:

> (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.

W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013), quoting Loving, 86 Fed. Cl. at 144. The last three elements are derived from Althen, 418 F.3d at 1278.

A Loving analysis requires the special master to "evaluat[e] whether the vaccine made the person worse than the person would have been but for the vaccination. In doing so, the natural course of the disease must be considered." Locane v. Sec'y of Health & Hum. Servs., No. 99-589V, 2011 WL 3855486, at *10 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), *mot. for rev. den'd*, 99 Fed. Cl. 715 (2011), *aff'd*, 685 F.3d 1375 (Fed. Cir. 2012); see also Hennessey v. Sec'y of Health & Hum. Servs., No. 01-190V, 2009 WL 1709053, at *41-42 (Fed. Cl. Spec. Mstr. May 29, 2009), *mot. for review den'd*, 91 Fed. Cl. 126 (2010). Nonetheless, a petitioner is not required "to demonstrate an expected outcome and that her current-post vaccination condition was worse than such expected outcome." Sharpe v. Sec'y of Health & Hum. Servs., 964 F.3d 1072, 1081 (Fed. Cir. 2020). Rather, the test "only requires a comparison of a petitioner's current, post-vaccination condition with her pre-vaccination condition." Id.

If a petitioner satisfies the Loving prongs, the burden shifts to the government to prove by preponderant evidence that "factors unrelated to the administration of the vaccine" caused the petitioner's injuries. 42 U.S.C. § 300aa–13(a)(1)(A)–(B). If the government does not carry its burden, the petitioner is entitled to compensation.

II. Factual Background

A. Mr. Gapen's Pre-Vaccination Medical History

On June 23, 2015, Mr. Gapen presented at Fairview Clinics. Exhibit 4 at 13. The reason for the visit was a rash on his right leg for "15+ years" and warts on his right hand. He was diagnosed with lichen simplex chronicus and was prescribed triamcinolone. Id. at 13-16. An asthma test was performed. He returned on July 10, 2015 for wart evaluation and treatment. Id. at 22-26.

Sometime in January of 2016, Mr. Gapen began experiencing concerning symptoms. On February 12, 2016, Mr. Gapen returned to Fairview Clinics feeling sick. Exhibit 4 at 38. In the subjective portion of the record, concerns included vomiting, gas, upper abdominal pain, weight loss of 20 pounds, and lightheadedness. The duration was listed as "1 month." Id. at 39. Occasional diarrhea was noted but profound blood in stool was denied. Id. at 40. Mr. Gapen had a fever (temperature of 100.8°F) and elevated heart rate (103 bpm). Exhibit 4 at 39; 53. The physician's assistant noted "[r]ecent ct scan revealed mild changes suggestion of colitis." Id. Universal ulcerative colitis with rectal bleeding was listed under patient's diagnosis / active problem list. Id.

Ulcerative colitis, a subtype of inflammatory bowel disease, is a chronic inflammatory disease of the intestine. Exhibit C (Dr. Longman's expert report) at 3. Medication can be used to treat UC but there is no known medical cure. Treatments include mesalamines (e.g. Lialda), steroids (e.g. prednisone), various immunosuppressives, and biologic therapies (e.g. anti-TNFα therapies, such as Humira). Though many patients benefit from medical treatments, development of relapsing disease is common. Id.

During the February 12, 2016 visit, various samples were collected and tests were ordered. Exhibit 4 at 41-47. Results revealed Mr. Gapen's erythrocyte sedimentation rate ("ESR") was 63 with a reference range of 0 – 15 mm/h, tagged as abnormal. Id. at 50. Hemoglobin levels were 9.0 g/dL with a reference range of 13.3 – 17.7 g/dL. Hematocrit was 28.7% with a 40.0 – 53.0 % reference range. Id.

at 49. Occult blood in stool was noted. Id. at 44, 47. Elevated white blood cell ("WBC") count and acute anemia were noted. Id. at 54.

The healthcare provider referred Mr. Gapen to gastroenterology for further assessments. Id. He was prescribed prednisone with a dose that tapered from 80 mg during the first few days to 10 mg during days 17-20. Id. at 42. Prednisone is a strong and fast-acting corticosteroid. It is effective for treating inflammation but does not cure the underlying disease. Exhibit A (Dr. Maverakis's expert report) at 9-10.

On February 22, 2016, Mr. Gapen presented to Minnesota Gastroenterology for a consultation and was seen by Dr. Daniel Van Handel. Exhibit 5 at 1. According to the history provided here, Mr. Gapen's abdominal pain, nausea, bloody diarrhea, and related symptoms began in late December 2015. Dr. Van Handel assessed Mr. Gapen as suffering colitis, reduced Mr. Gapen's tapering prednisone dosages, and scheduled a colonoscopy for the following week. Id. However, Dr. Van Handel noted: "Unfortunately, corticosteroids [were] started prior to diagnosis being confirmed or extent of the disease being evaluated. . . . Hopefully, a colonoscopy within one week will help confirm the diagnosis prior to further medical management decision[s]." Exhibit 5 at 1. In other words, in reducing inflammation, prednisone may have masked a more severe disease.

During the February 22, 2016 visit, Dr. Van Handel discussed various treatment options, including Lialda, for Mr. Gapen to read about. Exhibit 5 at 2. However, the treatment notes from the February 22, 2016 and February 25, 2016 visits do not clearly indicate Mr. Gapen was prescribed Lialda at those times.

Mr. Gapen underwent a colonoscopy on February 25, 2016. Id. at 8-9. The preliminary impressions were colitis and colon polyp. Id at 8. A May 25, 2016 record from Dr. Van Handel described the colonoscopy as showing "panulcerative colitis." Id. at 12. Dr. Van Handel continued the prednisone treatment, prescribing three 10 mg tablets per day. Id. at 9.

Mr. Gapen discontinued or finished his prednisone treatment around April 24, 2016. Exhibit 5 at 12 (Dr. Van Handel noted in a May 24, 2016 record that Mr. Gapen "has been off prednisone for one month").

B. Mr. Gapen's Medical History within Six Months of Vaccination

On May 24, 2016, Mr. Gapen returned to Minnesota Gastroenterology. Exhibit 5 at 12-14. At this visit, he received the Pneumococcal conjugate PCV-13 vaccination in his left deltoid. He maintains this vaccination caused long-lasting health problems.

Multiple metrics from the May 24, 2016 visit suggest Mr. Gapen's overall health was improving since February 2016. Mr. Gapen's hemoglobin levels had increased from 9.0 g/dL to 10.3 g/dL. Exhibit 5 at 18-20. WBC and CRP levels were normalizing. He had gained back twenty pounds of lost weight. Id. at 12. No diarrhea or abdominal pain were noted. Blood work was "notable for iron deficiency anemia." Exhibit 5 at 18. Mr. Gapen had pain in one knee, attributed to a torn ACL, "though no other joint pain." Id. at 12.

Mr. Gapen's leg rash was present and treated with Hydrocortisone cream and he received two iron infusions for quick treatment. Exhibit 5 at 18. Mr. Gapen was also instructed to take other medications for further UC management.

In their briefs, the parties state that on this date (May 24, 2016), Mr. Gapen "was started on Lialda." Pet'r's Br., filed July 26, 2021, at 6; Resp't's Br., filed Oct. 1, 2021, at 3; but see Exhibit A at 10 (Dr. Maverakis arguing Lialda treatment started after the February 25, 2016 colonoscopy).[3] Lialda is used to control UC flareups; on May 24, 2016, Mr. Gapen was instructed to "continue" taking Lialda for 6 months before tapering. Id. at 12.

Three days later, on May 27, 2016, Mr. Gapen went to work an early shift at Target. Exhibit 3 (affidavit). He left Target by 9:00 A.M. due to swelling, pain, and difficulty walking. Id. at 2. Mr. Gapen presented to the emergency department Allina Health – Unity Hospital in Fridley, Minnesota, where he remained for a few days. Id.

Mr. Gapen reported he developed a fever and hives on his legs and testicles the day prior (May 26, 2016). Exhibit 6 at 1. The rashes were later described (on

[3] The May 24, 2016 record states following: "He has been off prednisone for one month. He *was* started on Lialda 4.8 g daily." (*emphasis* added). Exhibit 5 at 12. Under Assessment/Plan, the record states "*Continue* Lialda 4.8 g daily." (*emphasis* added). Id. at 13. Later, Dr. Van Handel wrote: "Following the colonoscopy, Adam was weaned off of prednisone and continued on Lialda. He was given Prevnar-13 vaccine at this visit as well." Id. at 24 (Sept. 6, 2016 record). Thus, it is unclear whether the Lialda treatment began before or contemporaneously with vaccination.

May 30, 2016) as "quarter-sized, ring-like, circular rashes, slightly painful but not itchy." Id. at 13. Myalgias and sore throat were reported, and abdominal pain and diarrhea were denied. Id. Sepsis protocols were initiated. Id. at 3, 10. The attending ED physician, Dr. Andrew Meister, noted "[i]t is unclear to me whether his symptoms are related to [the PCV-13] immunization or this is a separate process given that his symptoms did not appear until 2 days after injection." Id. at 3. Similarly, Dr. Joudat Yazigi noted "it is not very clear whether it is an adverse reaction to pneumococcal vaccine which per literature would include most of the above listed symptoms versus sepsis/SIRS." Id. at 10. Assessments included "sepsis" and "suspected adverse reaction to pneumococcal vaccine." Id. "[P]ossible sepsis/hives/autoimmune response" is listed on a nurse's admission note. Id. at 16. An infectious disease consultation was scheduled.

The following day, on May 28, 2016, Mr. Gapen had an infectious disease consultation. Exhibit 6 at 12. Dr. Shewangizaq Worku diagnosed Mr. Gapen with "[e]rythema multiforme related to PCV-13 vaccination." Id. In a separate notation, Dr. Worku stated Mr. Gapen "developed systemic inflammatory response with associated erythema multiforme-like rash." Id. at 14. Dr. Worku recommended Mr. Gapen resume mesalamine (Lialda) for UC / diarrhea treatment. Id.

On May 29, 2016, Mr. Gapen was discharged from the Allina Health emergency department. Exhibit 6 at 23. Most symptoms had resolved. The discharge diagnoses include "[a]cute sepsis immune response syndrome secondary to adverse reaction from pneumococcal vaccine," ulcerative colitis, anemia, and erythema multiforme. Id. Mr. Gapen was advised to continue taking mesalamine daily. Id. at 24.[4]

During a June 2, 2016 follow-up visit at Fairview Clinic, a treater noted "Serum sickness, subsequent encounter." Exhibit 4 at 62. Mr. Gapen was prescribed a high dose of prednisone. Id.; see also exhibit 3 (affidavit) at 2. No rashes or joint pains were noted at this visit.

Mr. Gapen received additional testing and bloodwork at Minnesota Gastroenterology on July 12, 2016. Exhibit 5 at 21. The results were overall acceptable, with hemoglobin levels increasing. Id.

[4] Dr. Jacob disputes the use of term sepsis here because the term "implies infection, which was ruled out during the hospitalization." Exhibit 9 at 4. A discharge summary states: "No infection was found." Exhibit 6 at 23.

In August of 2016, Mr. Gapen started college. Exhibit 3 at 2. Although he wished to work more, he worked one day a week at Target with the option to leave early if needed. Id.

On August 4, 2016, via referral from Dr. Van Handel, Mr. Gapen saw Dr. Susan Leonard, for a rheumatology evaluation at Arthritis and Rheumatology Consultants. Exhibit 7 at 1; exhibit 3 at 2. Mr. Gapen was evaluated for joint pain and elevated c-reactive protein. Id. Dr. Leonard diagnosed Mr. Gapen with inflammatory polyarthropathy. Id. at 4. Dr. Leonard noted:

> I think this is highly likely inflammatory arthritis and tendinitis associated with the colitis. His colitis is active. He did calm down[] [a]fter he finished the long course of prednisone from February to March and started Lialda. However, it was about 6-8 weeks after going off the prednisone his bowels started to flare up and cause more diarrhea and bloody stools . . . Inflammatory arthritis associated with the colitis generally flares when the colitis is active . . . I think he needs stronger treatment for his bowel disease . . . I suspect something like Humira would be much more beneficial in him . . . [I] think inflammatory arthritis associated with [colitis] is much more likely and this also could be causing the skin rashes. . . . I don't think the inflammatory arthritis [is] secondary to the pneumonia vaccination.

Id. at 3-4.

Mr. Gapen had a follow-up appointment with Dr. Van Handel on September 6, 2016. Under past medical history, Dr. Van Handel wrote Mr. Gapen had previously been diagnosed with Stevens-Johnson syndrome ("SJS") secondary to Prevnar vaccine. Exhibit 5 at 24.[5] Although Dr. Leonard thought Mr. Gapen's hospitalization was related to the UC, Dr. Van Handel wrote he was uncertain "whether [Mr. Gapen's] joint symptoms are secondary to inadequate control of ulcerative colitis particularly given his GI symptoms are actually much better controlled than at the time of diagnosis." Id. at 25. He was again prescribed prednisone daily followed by a tapering dose to manage his symptoms. Id. Dr.

[5] The parties agree that Mr. Gapen did not suffer Stevens-Johnson syndrome and that this assertion is not corroborated by the other medical records.

Van Handel discussed checking insurance coverage for Humira and/or azathioprine. Id. A follow-up and colonoscopy were recommended.

On September 15, 2016, colon biopsies were performed and samples were collected. Exhibit 5 at 34. Findings included "inactive chronic colitis consistent with ulcerative colitis" and "mildly active chronic colitis consistent with ulcerative colitis." Id. Impression notes state "ulcerative pancolitis without complication." Id.[6]

In late September 2016, Mr. Gapen broke out in a painful rash, prompting him to call his parents to pick him up from college. Exhibit 3 (affidavit) at 2-3.

On October 13, 2016, Mr. Gapen had a follow-up appointment with Dr. Van Handel. Exhibit 5 at 38. The record states that Mr. Gapen was started on azathioprine 50 mg daily after the September 15, 2016 colonoscopy, but the drug was discontinued at this visit because Mr. Gapen reported "'foggy' mentation, headaches, and blurry vision" shortly after starting. Id. It further states he had joint aches and swelling a week prior. The note suggests Mr. Gapen was started on Humira 48 hours prior (October 11, 2016).[7]

Dr. Van Handel wrote that Mr. Gapen's UC "is complicated with what is thought to be severe inflammatory arthritis . . . [i]nterestingly, his symptoms of arthritis began after his GI symptoms were actually in clinical remission." Id. at 39. The record states Mr. Gapen was feeling better than he had in several months. Id. at 38.

C. Mr. Gapen's Medical History Six Months After Vaccination

[6] Dr. Van Handel's October 13, 2016 record states that after the September 15, 2016 colonoscopy, Mr. Gapen "was begun on azathioprine 50 mg daily with a plan to begin Humira in two to three weeks. He reports 'foggy' mentation, headaches, and blurry vision beginning shortly after azathioprine." Thus, the undersigned finds Mr. Gapen was started on azathioprine on September 15, 2016.

[7] In Mr. Gapen's affidavit, he states that Dr. Van Handel suggested he try Humira on October 4, 2016. Exhibit 3 at 3. Mr. Gapen reported that Humira started working on his symptoms "slowly but surely". Id. But, there does not appear to be a medical record documenting this discussion.

Mr. Gapen underwent a repeat colonoscopy and flexible sigmoidoscopy on December 13, 2016. Exhibit 5 at 42. The results revealed "mildly active chronic colitis consistent with ulcerative colitis." Id. Mr. Gapen reported experiencing joint aches at this visit. Id. at 44-47. Via affidavit, Mr. Gapen stated his swelling was almost completely gone in March of 2017. Exhibit 3 at 3. By self-report, subsequent flareups were "much milder." Id.

Between December 2016 and December 2017, it appears that Mr. Gapen did not seek medical attention for either GI or arthritic symptoms. The lack of medical records from this time suggests that Mr. Gapen's condition was controlled.[8] Mr. Gapen stated that after months of taking Humira, around March of 2017, the swelling had almost completely resolved. Exhibit 3 at 3.

Mr. Gapen suffered from some mental health issues in 2017. Exhibit 3 at 3-5. Depression and anxiety had contributed to difficulty with school and work. Id. Mr. Gapen reports these problems escalated in December of 2017. Id. at 4. He was admitted to Allina Health on December 15, 2017 for worsening anxiety, depression, and suicidal thoughts. Exhibit 6 at 226; exhibit 3 at 4.

On December 20, 2017, Dr. Van Handel recorded that Mr. Gapen's mental health issues had "dramatically improved" but noted ongoing joint aches and swelling. Exhibit 5 at 46. Overall, Mr. Gapen's health appeared to be improving. His biopsies were unremarkable. Id.

On January 2, 2018, Mr. Gapen returned to Fairview Clinics for a depression follow-up visit. Exhibit 4 at 74. The record states: "Gi [sic] apparently feels the arthritis is related to his serum sickness rxn to the Prevnar vaccine 1.5 yrs ago. Previous rheumatologist felt it was extra-disease manifestation of his UC. Gi feels it's not as he has been in remission for a while now on humira." Id. at 75.[9] It also notes daily pain involving his hands and feet, with some stiffness and soreness.

Experiencing arthritic pain, Mr. Gapen saw a new rheumatologist, Dr. Nitika Ghattaura, on February 13, 2018. Exhibit 10 at 3. Dr. Ghattaura wrote Mr. Gapen's physical exams suggest underlying arthritis, which can be related to UC.

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[8] In their briefs, neither party discusses the time period between December 2016 and December 2017. Pet'r's Br. at 8; Resp't's Br. at 6-7. Subsequent mental health issues, mild UC flares, and joint/arthritic pain are briefly discussed.

[9] "Gi" here likely refers to a gastrointestinal specialist. In context, "Gi" might refer to a treater at Fairview Clinics or Dr. Van Handel, and rheumatologist likely refers to Dr. Leonard.

Dr. Ghattaura further noted: "He might have gotten serum sickness like reaction to Prevnar vaccine but those symptoms should not persist even a year later." Id. at 4.

Mr. Gapen next sought treatment for arthritic pain on May 1, 2018. Exhibit 10 at 29. The record notes he had no significant swelling at that time, but he did complain of joint aches and stiffness. Id. at 31. Dr. Ghattaura wrote Mr. Gapen's "clinical picture is suggestive of seronegative inflammatory arthritis." Id. Plaquenil was prescribed for treatment. Id. at 32. Mr. Gapen reported on August 21, 2018 that his joint pains and stiffness were improving since starting Plaquenil. Id. at 54. Then on November 20, 2018, Mr. Gapen returned to Dr. Van Handel and reported "near complete resolution of joint aches in his hands, elbows, wrists, shoulders, and knees and back." Exhibit 15 at 11.

On May 7, 2019, Mr. Gapen had a follow-up colonoscopy. Exhibit 15 at 14. The findings note mucosal healing throughout the colon with no inflammation seen. Id. During a June 3, 2019 follow-up, Dr. Van Handel recorded Mr. Gapen's UC was "in clinical and endoscopic remission on Humira every 10-day dosing." Id. at 21.

On August 27, 2019, Mr. Gapen was seen by Kyle Olson, PA-C for evaluation of joint pains. Exhibit 51 at 106. In recounting Mr. Gapen's medical history, the record states his symptoms were attributed "to possible serum sickness-like reaction". Id. Regarding recent issues, it states he was having joint pain flareups "once every 1 to 2 weeks. The episode lasted for about 2 to 3 days." Id. Overall improvement was reported.

On October 28, 2019, Mr. Gapen was evaluated by Megan McGuigan, PA-C for "possible" SJS. Exhibit 51 at 93. The treater "would favor the etiology of arthralgias to be from his UC, even though his [symptoms] are controlled with Humira." Id. at 94.

Mr. Gapen was evaluated by Dr. Van Handel on July 1, 2020. Exhibit 52 at 6. Dr. Van Handel opined that Mr. Gapen's inflammatory arthropathy is thought to be secondary to SJS, secondary to PCV-13 vaccine. The record again reports clinical and endoscopic remission and that Mr. Gapen was on Humira and Lialda daily. Similarly, Dr. Ghattaura recorded Mr. Gapen's UC was in remission following a December 4, 2020 telemedicine visit. Exhibit 51 at 46-47.

III. Procedural History

Mr. Gapen filed his petition on March 21, 2019. Medical records were filed on March 25, 2019, along with an affidavit filed as exhibit 3. Additional records were identified and then filed on September 13, 2019. Subsequently, the Secretary of Health and Human Services ("the Secretary" or "respondent") filed his Rule 4(c) report, recommending against compensation. Resp't's Rep., filed Sept. 16, 2019.

The parties were advised to retain experts and provide them with instructions for their reports. See orders, issued Oct. 3, 2019 and Oct. 24, 2019. On December 18, 2019, Mr. Gapen filed a supplemental affidavit as exhibit 17.

On January 6, 2020, Mr. Gapen filed an expert report from Dr. Jerry Jacob as exhibit 19. Dr. Jacob opined that Mr. Gapen did not develop erythema multiforme or Stevens-Johnson syndrome. In Dr. Jacob's assessment, Mr. Gapen suffered an SSLR that aggravated his UC. New expert instructions were issued in light of the new diagnosis and significant aggravation claim. See orders, issued Jan. 27, 2020 and Feb. 26, 2020.

Subsequently, on May 4, 2020, Mr. Gapen filed his amended petition, pleading a significant aggravation of his underlying UC. Am. Pet., filed May 4, 2020, at 1. The same day, Mr. Gapen filed an expert report from Dr. John Santoro as exhibit 31. Dr. Santoro opined the PCV-13 vaccine caused Mr. Gapen to develop an SSLR and a subsequent significant aggravation of his underlying UC. Dr. Santoro also signaled that molecular mimicry played a role in Mr. Gapen's medical complications.

On October 2, 2020, the Secretary filed expert reports from Dr. Emanual Maverakis as exhibit A and Dr. Randy Longman as exhibit C, responding to Mr. Gapen's experts. Dr. Maverakis opined that Mr. Gapen had severe UC which was not well controlled until starting Humira, and that Mr. Gapen's symptoms are better explained by his underlying disease. Dr. Longman concurred, explaining UC management and why IBD associated joint inflammation explains Mr. Gapen's post-vaccination symptoms. Both experts disputed the logic of Mr. Gapen's SSLRs theory.

In the subsequent status conference, the undersigned informed Mr. Gapen that Dr. Santoro had passed away. Mr. Gapen indicated that he would file another expert report. See order, issued Oct. 26, 2020.

On December 22, 2020, Mr. Gapen filed a supplemental report from Dr. Jacob as exhibit 45. In a status report the same day, Mr. Gapen indicated he would retain another expert to substitute for Dr. Santoro. ECF 51. However, in a subsequent status report, Mr. Gapen stated he would not be filing any more expert reports and instead moved for a determination of entitlement based on the record. See Pet'r's Status Rep., filed Mar. 19, 2021.

As such, the undersigned issued a briefing order on April 13, 2021. Mr. Gapen filed additional medical records on May 28, 2021. Mr. Gapen filed his brief, stylized as a motion for a ruling on the record, on July 26, 2021. Mr. Gapen's brief is 25 pages and discussed only a few of the articles his experts cited. The Secretary filed his response on October 1, 2021. The Secretary's brief is 46 pages and thoroughly discusses the articles relied on by Mr. Gapen's experts. Mr. Gapen filed a 5-page reply on November 1, 2021.

IV. Summary of Expert Witnesses' Qualifications and Opinions

A. Petitioner's Expert, Dr. Jerry Jacob

Mr. Gapen submitted reports from Jerry Jacob, a specialist in infectious diseases. Dr. Jacob is board-certified in internal medicine and infectious diseases. He is a practicing infectious disease physician. Exhibit 20 at 2; exhibit 19 at 1. He is an assistant professor of clinical medicine at the University of Pennsylvania. Exhibit 19 at 1. Dr. Jacob's first report, exhibit 19, will be discussed prior to his responsive report, exhibit 45.

Initially, Dr. Jacob summarizes Mr. Gapen's pertinent medical history. Exhibit 19 at 2-5. Next, Dr. Jacob reviews potential diseases discussed during the course of Mr. Gapen's treatment. Erythema multiforme ("EM") and Stevens-Johnson Syndrome ("SJS"), Dr. Jacob explains, are disorders of the skin and/or internal lining of body cavities, resulting from damages caused by the immune system, often triggered by infections or drugs. Exhibit 19 at 6.

Serum sickness, he explains, is characterized as an acute reaction mediated by the immune system "that occurs 1-2 weeks after exposure to a non-human protein (eg, sheep anti-venom used for snakebites) with cardinal features of fever, rash, and arthralgia." Exhibit 19 at 9. Dr. Jacob notes the rashes often consist of "hive-like lesions that gradually expand, leaving a central clearing or central purple color, and most evident on the abdomen or lower legs." Id. at 10; exhibit 30

(Wener).[10] Dr. Jacob asserts that prior exposure to the protein can promote a quicker reaction. Id. at 9-10. An SSLR is an acute reaction with similar clinical findings. However, Dr. Jacob explains it is caused by different mechanisms and typically occurs in response to medication. Id. at 10.

Dr. Jacob also notes that SSLRs have "some overlapping clinical findings and pathogenic mechanisms" to cutaneous vasculitis, "which has been reported in association with ulcerative colitis." Id. at 10. Furthermore, universally accepted diagnostic criteria for SSLR (and serum sickness) do not exist. Id. Diagnosis is often based on finding rash, fever, arthralgias, and myalgias manifesting with temporal relation to a potential inciting agent.

To differentiate the diagnoses, Dr. Jacob reviewed medical literature discussing EM, SJS, and dermatologic issues. See exhibits 21-27. Dr. Jacob opines the lesions on Mr. Gapen's thighs have features suggestive of purpura and concludes they do not resemble the lesions defined in the EM literature. Exhibit 19 at 11. Similarly, the lesions are inconsistent with manifestation of SJS. Id. For these and other reasons, Dr. Jacob concludes Mr. Gapen did not suffer from EM or SJS.

Rather, Dr. Jacob assesses Mr. Gapen's presentation as most consistent with an SSLR. Dr. Jacob notes that drugs are the primary etiology for SSLRs, and that SSLRs typically have a short duration. Id. at 10-11. As such, he opines the prolonged hospitalization course is better explained "by a flare of an extraintestinal manifestation of ulcerative colitis (eg, cutaneous vasculitis and/or IBD associated arthritis)." Id. In other words, Dr. Jacob indicates Mr. Gapen developed an SSLR which prompted his hospitalization, and his subsequent treatment and relapses are due to an exacerbation of his UC. Id. at 12.

Dr. Jacob provides medical literature in support of his position. SSLRs have been associated with rabies vaccines, and, less often, with influenza, tetanus, and pneumococcal vaccines. Id. at 10; exhibit 28 (Hengge et al. letter to editor);[11] exhibit 29 (Chiong et al. case report).[12]

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[10] Mark H. Wener, *Serum sickness and serum sickness-like reactions*, UpToDate, Post, TW (Ed) (2014).

[11] Hengge UR, et al., *Severe serum sickness following pneumococcal vaccination in an AIDS patient*, 17 INT'L J. OF STD & AIDS 210 (2006).

B. Petitioner's Expert, Dr. John J. Santoro

Mr. Gapen also presented a report from a second expert, John J. Santoro, a gastroenterologist. Before the opportunity to submit a responsive report, Dr. Santoro had passed away in 2020. See order, issued Oct. 26, 2020. Dr. Santoro was board-certified in internal medicine and gastroenterology. Exhibit 32 at 2. His practice focused on treating inflammatory bowel disease ("IBD") and he held a clinical associate professorship at Rowan University School of Osteopathic Medicine. Exhibit 31 at 1-2.

After summarizing the relevant medical history, Dr. Santoro's report provides background on IBD and two of its major subsets, UC and Crohn's disease ("CD"). Exhibit 31 at 6-7. Dr. Santoro explains that UC is a chronic inflammatory bowel disease characterized by inflammation of the large intestine. Id. at 6. When the inner lining of the intestine becomes inflamed, ulcers may form on the surface. Id. As such, the extraintestinal manifestations can affect the skin, eyes, and joints. Id. The inflammation can range from mild to severe, causing abdominal pain and diarrhea. The exact cause(s) of IBD are not known. Similarly, the pathogenesis of UC and its flares is not clear, though some argue "that loss of tolerance against the indigenous enteric flora is the central event in IBD pathogenesis." Id. The clinical course of UC can range from "a quiescent course with prolonged periods of remission to fulminant disease requiring intensive medical treatment or surgery." Id. at 11. Stopping a medication that is controlling the disease can result in an exacerbation. Id.

Dr. Santoro next discusses molecular mimicry as a mechanism that may cause autoimmune diseases after vaccination. Id. at 7-9. In this context, Dr. Santoro discusses a case report regarding cytophagic histiocytic panniculitis after H1N1 vaccination. Exhibit 38 (Pauwels et al. case report).[13] Dr. Santoro also notes reports of several flares of pre-existing IBD in patients who received an HPV vaccination. Exhibit 40 (Jacobson et al.).[14] Dr. Santoro also cites the Gardasil

[12] Fabian J.K. Chiong, et al., *Serum sickness-like reaction after influenza vaccination*, BMJ CASE REP 1 (2015). This article was also submitted as exhibit 49.

[13] C. Pauwels, et al., *Cytophagic Histiocytic Panniculitis after H1N1 Vaccination: A Case Report and Review of the Cutaneous Side Effects of Influenza Vaccines*, 222 DERMATOLOGY 217 (2011).

vaccine package insert, which reports autoimmune diseases during the post-marketing experience.

According to Dr. Santoro's analysis, the PCV-13 vaccine triggered an autoantibody against Mr. Gapen's intestinal epithelial cells via molecular mimicry. Id. at 9. Dr. Santoro opines that molecular mimicry may cause the exacerbation of IBD within one to twenty weeks after vaccination. Id. at 10.

Dr. Santoro also endorses Dr. Jacob's SSLR theory, suggesting an SSLR accounted for an "ongoing" exacerbation of Mr. Gapen's UC. Id. In support, Dr. Santoro references a case report of a serum sickness-like syndrome as the first manifestation of IBD, in which laboratory findings suggested immune complex formation as the cause of the issue. Id. at 9-10; exhibit 42 (Kaddourah et. al).[15] Dr. Santoro explains that "immune complex formation with complement activation often plays a key role in the pathophysiology of [SSLRs]. . . ." Exhibit 31 at 10.

In sum, Dr. Santoro argues that pre-vaccination, Mr. Gapen had well controlled colitis in remission and was in "perfectly good health." Exhibit 31 at 4. After the PCV-13 vaccination, Dr. Santoro opines, Mr. Gapen's UC flares were significantly altered, representing a substantial aggravation of the underlying condition. Dr. Santoro notes the rashes and arthritic pain were more persistent after vaccination and that Mr. Gapen's mental health deteriorated.

C. Respondent's Expert, Dr. Emanual Maverakis

The Secretary submitted a report from Dr. Emanual Maverakis, an immunologist. Exhibit A at 1. Dr. Maverakis is board-certified in dermatology. Exhibit B at 2. He specializes in seeing patients with immune mediated diseases, and holds a professorship at the University of California, Davis. Exhibit A at 1.

Dr. Maverakis's summary of Mr. Gapen's medical history is mostly congruent with petitioner's experts' recitations. Exhibit A at 3-8. However, the parties' positions diverge with their interpretations of the medical records.

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[14] Denise L. Jacobson, 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] Osama Kaddourah, Mouhanna A. Ghanimeh & Fadi Hamid, *A case report of serum sickness-like syndrome as the first manifestation of inflammatory bowel disease IBD*, 3 AM. J. DIGEST. DIS. 38 (2016).

To start, Dr. Maverakis disagrees with the assessments that Mr. Gapen was in good health prior to vaccination. Instead, Dr. Maverakis indicates Mr. Gapen had residually active *severe* ulcerative colitis and "was especially poised to have a rebound flare of his disease." Exhibit A at 9-10. For support, Dr. Maverakis references the Truelove and Witts criteria, which are used to grade the severity of UC. Exhibit A tab 2 (Truelove & Witts).[16] These criteria are utilized by the American Gastroenterological Association ("AGA"). Exhibit A tab 1 (Ko et al.).[17] The Truelove manuscript assesses "severe" ulcerative colitis by the following criteria:

> Severe diarrhoea [sic] (six or more motions a day) with macroscopic blood in stools. Fever (mean evening temperature more than 99.5° F. (37.5° C.), *or* a temperature of 100° F. (37.8° C.), or more on at least two days out of four). Tachycardia (mean pulse rate more than 90 per minute). Anaemia [sic] (haemoglobin [sic] 75% or less—allowance made for recent transfusion. E.S.R. much raised (more than 30 mm. in one hour).

In contrast, "mild" UC is characterized by "Mild diarrhoea [sic] (four or less motions a day) with no more than small amounts of macroscopic blood in stools. No fever. No tachycardia. Anaemia [sic] not severe. E.S.R. not raised above 30 mm. in one hour." Finally, "moderately severe" is defined as an intermediate between mild and severe.

With these definitions, Dr. Maverakis next points to Dr. Van Handel's February 22, 2016 records. Dr. Van Handel recorded that in late December 2015, Mr. Gapen had "abdominal pain in the lower quadrants, nausea, bloody diarrhea, urgency, and mucus discharge per rectum. He lost 20 pounds." Exhibit 5 at 1. Although the number of motions per day and the amount of blood in stools is not provided, Dr. Maverakis offers this record as support that Mr. Gapen had severe ulcerative colitis. In addition, Dr. Maverakis highlights Mr. Gapen's February 12, 2016 visit to Fairview Clinics, in which occult blood in stool was noted. Exhibit A

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[16] S.C. Truelove & L.J. Witts, *Cortisone in Ulcerative Colitis Final Report on a Therapeutic Trial*, 2 BR. MED. J. 4947 (1955).

[17] Cynthia Ko et al., *AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis*, 156 GASTROENTEROLOGY 748 (2019).

at 9. During that visit, Mr. Gapen presented with fever (100.8°F), tachycardia (heart rate of 103 bpm), decreased hemoglobin levels, and raised E.S.R. Exhibit A at 9; exhibit 4 at 39, 49, 53. Comparing these values to the AGA criteria, Dr. Maverakis opines that Mr. Gapen had active severe UC at the time of his vaccination, despite not presenting external symptoms. Exhibit A at 12.

Dr. Maverakis also discusses the difficulty of determining the disease's severity. Dr. Maverakis argues that by the time Mr. Gapen was evaluated by Dr. Van Handel on February 22, 2016, Mr. Gapen's visible symptoms had largely resolved. Exhibit A at 9. Dr. Maverakis attributes the improvement to the prednisone that Mr. Gapen started taking about 10 days before the February 22, 2016 appointment with Dr. Van Handel.[18] For additional support, Dr. Maverakis cites to Dr. Van Handel, who noted: "Unfortunately, corticosteroids [were] started prior to diagnosis being confirmed or extent of the disease being evaluated. . . . Hopefully, a colonoscopy within one week will help confirm the diagnosis prior to further medical management decision[s]." Exhibit 5 at 1; exhibit A at 10.

Dr. Maverakis opines the February 25, 2016 colonoscopy, which Dr. Van Handel interpreted as evincing "panulcerative colitis," suggests extensive disease throughout the colon. Exhibit A at 10; exhibit 5 at 12. Dr. Maverakis bolsters this impression with the biopsies of the ascending, transverse, and descending colon, which showed mildly to moderately active chronic colitis consistent with UC. Exhibit 5 at 10; exhibit A at 10. Thus, although symptoms appeared to have largely resolved, Dr. Maverakis opines Mr. Gapen was not in good health at this time. Dr. Maverakis notes that many patients considered to be in clinical remission actually have persistent endoscopic inflammation. Exhibit A at 10; exhibit A tab 3 (Moss article), at 1-2.[19]

Furthermore, Dr. Maverakis explains Mr. Gapen was likely to experience disease exacerbation due to Mr. Gapen's transitioning treatment course. Exhibit A at 10-11. Dr. Maverakis opines that starting February 25, 2016, Mr. Gapen was taking two immunosuppressive agents: a tapering dose of prednisone and a high dose of Lialda. "While his symptoms appeared to be well-controlled on

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[18] Prednisone is a strong anti-inflammatory agent and a fast-acting immunosuppressive agent. Exhibit A at 9-10. Long term use of prednisone is associated with deleterious effects and thus it is generally not recommended for long-term management of UC. Id.

[19] Alan C. Moss, *Residual Inflammation and Ulcerative Colitis in Remission*, 10 GASTROENTEROLOGY & HEPATOLOGY 181 (2014).

prednisone and mesalamine, the question remained would he be well-controlled on Lialda monotherapy." Exhibit A at 10. According to Dr. Maverakis, mesalamine is beneficial for mild to moderate UC, see exhibit A tab 1 (Ko et al.), at pdf 1, but mesalamine alone would not be effective for treating severe UC. Exhibit A at 11. Dr. Maverakis also references Ko et al. to note that certain disease features predict an aggressive disease course, even in patients who initially present with mild to moderate disease. Exhibit A at 10. These include "age younger than 40 years at diagnosis, extensive disease, severe endoscopic activity [ ] extra-intestinal manifestations, and elevated inflammatory markers." Exhibit A tab 1 (Ko), at pdf 1. For these reasons, Dr. Maverakis opines that following February 25, 2016, disease exacerbation was increasingly likely.

Next, the Secretary's expert responds to Dr. Jacob's assessment that Mr. Gapen's skin eruptions evince an SSLR. Dr. Maverakis agrees with Dr. Jacob that SSLRs are immune-complex mediated reactions that can present with fever, rash, and/or arthralgias. Exhibit A at 11. However, he argues the timing and chronicity are not consistent with serum sickness. For support, Dr. Maverakis points to a case study of health care providers, in which the median onset of serum sickness was 9 days after receiving a second dose of inactive influenza vaccine. Exhibit A tab 6 (Apisarnthanarak et al.), at pdf 2-3.[20] Another case series showed the average onset time of SSLRs was 10 days after a human diploid cell rabies vaccine ("HDCRV") booster. Exhibit A tab 7 (Warrington et al.), at pdf 3.[21] Dr. Maverakis notes it takes considerable time for an antibody response to develop and form immune-complexes and argues experiencing an SSLR two days after vaccination is incompatible with adaptive immunity principles. Exhibit A at 11. Dr. Maverakis further notes that SSLRs are documented to resolve within a few days and are not capable of being a chronic condition. See exhibits A tab 6 and A tab 7.

With these bases, Dr. Maverakis attributes Mr. Gapen's inflammatory arthritis and skin eruptions to his UC rather than the vaccination. Dr. Maverakis notes that extraintestinal joint manifestations are extremely common in UC

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[20] Anucha Apisarnthanarak et al., *Serum Sickness-Like Reaction Associated with Inactivated Influenza Vaccination among Thai Health Care Personnel: Risk Factors and Outcomes*, 49 CLINICAL INFECTIOUS DISEASES 18, 19-20 (2009).

[21] Richard J. Warrington et al., *Immunologic studies in subjects with a serum sickness-like illness after immunization with human diploid cell rabies vaccine*, 79 J. ALLERGY & CLINICAL IMMUNOLOGY 605, 607 (1987).

patients, "reportedly occurring in 29.8% of patients with pancolitis." Exhibit A at 12; exhibit A tab 8 (Rotstein, Entel & Zeviner);[22] exhibit A tab 9 (Dorofeyev, Vasilenko & Rassokhina), at pdf 1.[23] Dr. Maverakis points to Dr. Leonard's August 4, 2016 record for support. Dr. Leonard opined Mr. Gapen had inflammatory polyarthropathy associated with the colitis and discounted the potential for his inflammatory arthritis to be secondary to a vaccination. Exhibit A at 12; exhibit 7 at 3-4.

In sum, Dr. Maverakis opines Mr. Gapen had active UC at the time of vaccination, despite not presenting external symptoms. Dr. Maverakis argues a chronic serum sickness-like reaction occurring two days after vaccination is unlikely. By contrast, it is likely for patients with UC to manifest skin and joint symptoms associated with inflammation.

D. Respondent's Expert, Dr. Randy Longman

The Secretary also submitted a report from Dr. Randy Longman, a gastroenterologist. Exhibit C at 1. Dr. Longman is board-certified in internal medicine and gastroenterology. Id. He has provided direct care to over 3000 patients with inflammatory and non-inflammatory intestinal diseases. Id.

Dr. Longman's summary of pertinent facts is in accord with the other experts' summaries. Exhibit C at 2-3. Similarly, his summary of UC is in accord with Dr. Maverakis's summary. Exhibit C at 3-4.

Dr. Longman additionally notes factors that may predict the disease course and response to medical therapies. Patients diagnosed at younger ages have a lower likelihood of steroid-free remission. Id. at 3; exhibit C tab 1 (Ha et al.).[24] This is similar to the literature cited by Dr. Maverakis. Other features associated with a poor prognosis include "pan-colitis at diagnosis, severe endoscopic disease,

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[22] Jerome Rotstein, Irwin Entel & Barbara Zeviner, *Arthritis Associated with Ulcerative Colitis*, 22 ANN. RHEUM. DIS. 194 (1963).

[23] A.E. Dorofeyev, I.V. Vasilenko & O.A Rassokhina, *Joint extraintestinal Manifestations in Ulcerative Colitis*, 27 DIGESTIVE DISEASES 502 (2009).

[24] Christina Y. Ha et al., *Patients With Late-Adult-Onset Ulcerative Colitis Have Better Outcomes Than Those With Early Onset Disease*, 8 CLINICAL GASTROENTEROLOGY & HEPATOLOGY 682 (2010).

elevated CRP, and the need for hospitalization." Exhibit C at 3; see exhibit C tab 2 (Rubin et al.), at pdf 18.[25] Dr. Longman further notes that "deep remission" is the preferred outcome, which includes symptomatic remission as well as endoscopic healing. Id. at 4. Dr. Longman also discusses IBD associated spondyloarthritis, noting joint inflammation is a common symptom of IBD and that joint inflammation commonly occurs when intestinal symptoms and inflammation are active. Id. at 4, 6.

Next, Dr. Longman responds to Mr. Gapen's experts' theories, starting with SSLRs. In response to Dr. Santoro's statement that Mr. Gapen's "ongoing serum sickness like reaction" exacerbated his UC, Dr. Longman argues Mr. Gapen's prolonged post-hospitalization course and joint symptoms are "better explained" by UC and IBD-associated arthritis than vaccine-induced SSLR. Exhibit C at 5; exhibit 31 at 9 (Dr. Santoro's report). Dr. Longman argues there is no evidence the SSLR was ongoing, and notes that Dr. Santoro's position is in conflict with Dr. Jacob's report, which notes the pathogenesis of SSLR reflects a short duration. Exhibit C at 5; exhibit 19 at 11 (Dr. Jacob's report). Additionally, Dr. Longman argues the Kaddourah case report (raised by Dr. Santoro), in which SSLR was noted as a first manifestation of IBD, is not relevant because Mr. Gapen was diagnosed with UC prior to vaccination and any subsequent SSLR. Exhibit C at 5.

Dr. Longman next addresses molecular mimicry. He maintains the Pauwels case report of histiocytic panniculitis following flu immunization, raised by Dr. Santoro, does not support molecular mimicry in this case. Exhibit C at 5. The case report showed no evidence of clonal T-cell receptor rearrangement or expansion. Exhibit 38 (Pauwels et al. case report) at pdf 3. Dr. Longman thus argues this report shows no evidence of a specific T cell response and does not support molecular mimicry as a cause. Id.; see exhibit 38 at pdf 3. Additionally, Dr. Longman notes the authors also discussed thiomersal as a possible cause of immune response. Exhibit 38 at pdf 3. As such, Dr. Longman argues the case report is unrelated to Mr. Gapen's case.

In response to the Jacobson et al. article, in which several flares of pre-existing IBD occurred in patients who received HPV vaccination, Dr. Longman notes the following caveat from the authors: "both investigators and the [Data Safety Monitoring Board] felt that their hospitalizations were due to ongoing active disease, and that the vaccine was unlikely to have resulted in the hospitalizations."

[25] David T. Rubin et al., ACG Clinical Guideline: Ulcerative Colitis in Adults, 114 AM. J. GASTROENTEROLOGY 384 (2019).

Exhibit C at 5; exhibit 40 (Jacobson et al.) at 7. Furthermore, this reference is focused on HPV vaccines, not the PCV-13 vaccine. In sum, Dr. Longman argues "it is unclear how autoantibodies against epithelial cells would subsequently contribute to joint inflammation." Exhibit C at 6.

Although Dr. Longman does not discuss Mr. Gapen's prior condition in depth, he argues Mr. Gapen's UC was "incompletely controlled," and that Mr. Gapen's joint inflammation persists until controlled. Exhibit C at 6. Like Dr. Maverakis, Dr. Longman argues the initial improvement in clinical symptoms is attributable to prednisone, but intestinal inflammation remained active, as evidenced by clinical symptoms and the colonoscopy. Exhibit C at 6. "Although the petitioner's clinical symptoms improved following steroid therapy [exhibit 5 at 1], mesalamine therapy alone was insufficient to maintain long-term remission as evidenced by persistent iron deficiency anemia and thrombocytosis before vaccination [exhibit 5 at 18]." Exhibit C at 6. Dr. Longman references the September 6, 2016 record to show Mr. Gapen had active UC. The record noted 2-6 stools per day and the evaluation precipitated the start of anti-TNFα biologic therapy (Humira) to control his colitis. Exhibit C at 6; exhibit 5 at 24-25. Dr. Longman notes anti-TNFα therapy is recommended for treatment of IBD associated joint inflammation. Exhibit C at 7; exhibit C tab 3 (Kumar et al.), at pdf 7.[26]

With respect to timing, Dr. Longman argues the joint inflammation that Mr. Gapen developed and sustained following the PCV-13 vaccination is consistent with the natural history of UC and associated extraintestinal joint inflammation. Although initially attributed to Mr. Gapen's history of an ACL injury, Dr. Longman argues Mr. Gapen's knee pain in February 2016 (exhibit 5 at 1) was IBD-associated arthritis. Exhibit C at 6-7. Dr. Longman points to Dr. Leonard's August 2016 evaluation for support. Though Mr. Gapen had some improvement in clinical symptoms with prednisone, Dr. Longman states clinical symptoms and colonoscopy confirm Mr. Gapen's symptoms and intestinal inflammation remained active. Dr. Longman notes a subsequent examination in December 2016 showed improvement "despite persistent active chronic colitis" in biopsies. Exhibit C at 6; exhibit 5 at 42. As such, Dr. Longman opines that "petitioner's joint inflammation coincides with the onset of his intestinal inflammation and persists until inflammation is under control." Exhibit C at 6.

[26] Anand Kumar et al., *Defining the phenotype, pathogenesis and treatment of Crohn's disease associated spondyloarthritis*, 55 J. GASTROENTEROLOGY 667, 673 (2020).

E. Dr. Jacob's Supplemental Report

On December 22, 2020, Mr. Gapen filed a supplemental report from Dr. Jacob as exhibit 45. Expanding on the causation theory, Dr. Jacob states serum sicknesses are caused by immune complexes involving human antibodies and foreign protein(s). Id. at 1-2. However, Dr. Jacob notes the mechanism for SSLRs is not well understood. Id. at 2. Nonetheless, he notes again that SSLRs have been documented to occur after administration of some antibiotics and vaccines. (Exhibits 28, 29, 30). Dr. Jacob provides an article reviewing VAERS reports of events occurring after vaccination with 7-valent pneumococcal conjugate vaccine, which notes some reports of SSLRs within one day of vaccination. Exhibit 47 (Wise et al.).[27] Dr. Jacob also supplies a case report of an SSLR 1-2 days after an H1N1 vaccination. Exhibit 48 (Bonds & Kelly article).[28] Dr. Jacob also provides a letter to the JAMA editor regarding serum sickness and tetanus immunization. Exhibit 50 (Daschbach letter).[29]

Dr. Jacob emphasizes the opinions of the physicians that evaluated Mr. Gapen, many of which suggested an immunologic reaction to the PCV-13 vaccine occurred. Exhibit 45 at 3-4 (citing exhibit 5 at 1-4, 8-11, 12-15, 23-24). Furthermore, Dr. Jacob explains that while SSLRs typically resolve on their own within a few days, "a systemic inflammatory process related to an underling chronic disease would typically require a more prolonged course of therapy for recovery." Exhibit 45 at 4.

In summary, Dr. Jacob concludes the PCV-13 vaccine caused an SSLR 2-3 days after administration. This manifested as acute onset of fever, hives-like rashes, and ankle swelling. Dr. Jacob opines Mr. Gapen's UC was under control at the time of vaccination, and the vaccine is the likely "immediate cause of his symptoms." Exhibit 45 at 4. Dr. Jacob attributes Mr. Gapen's subsequent course to this inciting inflammatory process and its interaction with the underlying UC.

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[27] Robert P. Wise et al., *Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine*, 292 JAMA 1702 (2004).

[28] Rana S. Bonds & Brent C. Kelly, *Severe Serum Sickness After H1N1 Influenza Vaccination*, 345 AM. J. MED. SCI. 412 (2013).

[29] R. J. Daschbach, *Serum Sickness and Tetanus Immunization*, 220 JAMA 1619 (1972).

V. Summary and Assessment of the Parties' Arguments

The parties disagree in several key respects. First, they dispute Mr. Gapen's condition prior to vaccination, namely, the severity of his UC and the sufficiency of medications used during that time. Second, they disagree over Mr. Gapen's condition after vaccination. Mr. Gapen argues he suffered an SSLR shortly after vaccination, subsequently aggravating his UC such that he experienced new skin manifestations, protracted joint pains and swelling, and mental health problems stemming from his condition. The Secretary argues Mr. Gapen's UC was severe and inadequately controlled until starting Humira, naturally resulting in flares and arthritic pain (i.e. extraintestinal inflammatory manifestations of the UC). The Secretary further argues Mr. Gapen did not suffer an SSLR and that an SSLR cannot chronically aggravate UC. Third, the parties dispute the reliability of molecular mimicry to explain how a PCV-13 vaccine can aggravate UC. These topics are addressed below.

A. Mr. Gapen's Condition Prior To Administration Of The Vaccine

The parties agree that Mr. Gapen was diagnosed with UC prior to his vaccination.[30] However, the parties disagree over the severity of Mr. Gapen's condition and whether his condition was well controlled by the medications taken during this time. The analysis of this issue considers (1) the pertinent medical records, (2) Mr. Gapen's arguments as presented in reports from experts as well as briefs, and (3) the Secretary's arguments from his brief and expert reports. Based upon these factors, a conclusion is reached in section (4) below.

1. Recitation of Pertinent Medical Records

Mr. Gapen's medical history prior to the May 24, 2016 vaccination includes prior rashes (including a rash on his leg for "15+ years"), warts, and eczema, as well as ACL reconstruction. Notable problems began in early 2016.

On February 12, 2016, Mr. Gapen presented to Fairview Clinic, reporting a month history of vomiting, gas, upper abdominal pain, and 20 pounds of weight loss. Exhibit 4 at 38-39. Occasional diarrhea was noted but profound blood in stool was denied. Id. at 40. He had a fever and elevated heart rate, abnormally raised ESR levels and decreased hemoglobin. A CT scan revealed mild changes suggestive of colitis. Universal ulcerative colitis with rectal bleeding was listed

[30] Neither party opines as to precisely when Mr. Gapen developed UC.

under patient's diagnosis / active problem list. Id. Mr. Gapen was prescribed a tapering dose of prednisone, a strong and fast-acting drug, and was referred to gastroenterology.

Then on February 22, 2016, Mr. Gapen had his referral visit to Minnesota Gastroenterology, where he was evaluated by Dr. Van Handel. The record notes symptoms of urgency, bloody diarrhea, and weight loss since December 2015. This record is somewhat in conflict with the February 12, 2016 record which indicated the symptoms began sometime in January 2016. Nonetheless, it appears Mr. Gapen's UC was active in December 2015 or January 2016.

During the February 22, 2016 visit, Mr. Gapen was assessed with colitis, possible IBD. Mr. Gapen's prednisone dosage was tapered. However, the impression note states "[u]nfortunately, corticosteroids [were] started prior to diagnosis being confirmed or extent of the disease being evaluated." Exhibit 5 at 1. A colonoscopy was scheduled to help confirm diagnosis and inform further medical management.

Mr. Gapen underwent a colonoscopy on February 25, 2016. Id. at 8-9. The preliminary impressions were colitis and colon polyp. Id at 8. The assessment was mild-moderately active chronic colitis consistent with ulcerative colitis. Exhibit 5 at 10. A May 25, 2016 record from Dr. Van Handel described the colonoscopy as showing "panulcerative colitis." Id. at 12. Mr. Gapen continued taking the tapering doses of prednisone.

The medical records indicate Mr. Gapen discontinued / finished his prednisone treatment around April 24, 2016. Exhibit 5 at 12 (Dr. Van Handel noted in a May 24, 2016 record that Mr. Gapen "has been off prednisone for one month"). The next notable medical record is on May 24, 2016, the date of vaccination.

2. Petitioner's Position

In his brief, Mr. Gapen argues his "pre-existing condition (before the PCV-13 vaccination and alleged aggravation) was well controlled colitis- in remission on a tapering dose of Prednisone." Pet'r's Br. at 5. Mr. Gapen states that prior to 2016, his medical history was "remarkable only for asthma, eczema, ACL tear with reconstructive surgery, skin warts, and a right lower extremity rash diagnosed as lichen simplex chronicus in June 2015." Id.; exhibit 4 at 13-16, 22-26. He was active and attending college, but regularly seeing a doctor for UC problems.

Pet'r's Br. at 6; exhibit 17 at 1 (affidavit). He reports no similar rashes, swelling or pain around his body during this time. Pet'r's Br. at 6; exhibit 17 at 1-2. Mr. Gapen represented that prior to vaccination, he was in good health. Exhibit 3 at 1 (affidavit).

Dr. Santoro similarly stated Mr. Gapen "was in perfectly good health" and that his then-current medication "was working perfectly." Exhibit 31 at 4. Dr. Santoro opined he had "well controlled colitis- in remission". Id. at 12.

Mr. Gapen relies upon Dr. Van Handel's evaluation of him on the date of vaccination. Then, Dr. Van Handel wrote that Mr. Gapen was "quite pleased" with the control of his symptoms. Lab values showed improvements, including increased hemoglobin and platelet levels, normal CRP, and normalizing WBC. Pet'r's Br. at 21; exhibit 5 at 18-20. In sum, Mr. Gapen's position is that his UC was managed and in remission.

3. Respondent's Position

The Secretary disagrees with the assessments that Mr. Gapen was in good health and that his medications were working perfectly. Instead, the Secretary argues Mr. Gapen had residually active *severe* ulcerative colitis and "was especially poised to have a rebound flare of his disease." Exhibit A at 9-10; Resp't's Br. at 28-34.

Dr. Maverakis references the AGA criteria, which are used to grade the severity of UC. Dr. Van Handel recorded that in late December 2015, Mr. Gapen presented with "abdominal pain in the lower quadrants, nausea, bloody diarrhea, urgency, and mucus discharge per rectum. He lost 20 pounds." Exhibit 5 at 1. To Dr. Maverakis, this record suggests Mr. Gapen's UC was active then and that he was not in good health at that time. Dr. Maverakis argues Dr. Santoro's opinion (that Mr. Gapen was in good health) was premised on the assumption that Mr. Gapen's UC was adequately controlled by mesalamine monotherapy at the time of vaccination. In contrast, Dr. Maverakis argues the medications were masking a more severe disease state. Exhibit A at 8-11. Similarly, Dr. Longman states "the majority of patients respond to initial medical therapy, but develop relapsing disease." Exhibit C at 3; Resp't's Br. at 28. Prednisone can be used to induce remission but is not recommended for maintenance therapy. Exhibit C at 4.

Dr. Maverakis opines that Mr. Gapen's UC was also active at the time of his vaccination, despite not presenting external symptoms. Exhibit A at 12. Dr.

Longman argues Mr. Gapen's UC was "incompletely controlled." Exhibit C at 4, 6.

4. Conclusions

The divergence of opinions regarding Mr. Gapen's health prior to vaccination appears to be due to the fact that Mr. Gapen was receiving treatment for his UC. In other words, the treatment plan complicates an assessment of Mr. Gapen's health during this timeframe. As acknowledged by Dr. Van Handel, post-facto assessments are complicated by ongoing treatment protocols.

Nonetheless, the record on the whole supports the finding, on a more likely than not basis, that Mr. Gapen had moderately severe active UC prior to and at the time of vaccination. An evaluation of Mr. Gapen's health at multiple pre-vaccination milestones alongside discussion of UC generally follows. The undersigned considers (a) Mr. Gapen's initial UC flare using diagnostic criteria supplied by the experts, (b) the February 2016 colonoscopy, and (c) reports of improvement in May 2016.

a) Mr. Gapen's Initial UC Flare and Hospitalization

The initial flare in December 2015 / January 2016 led Mr. Gapen to seek treatment. The description of symptoms provided during the February 12, 2016 visit, based on the AGA criteria relied upon by Dr. Maverakis, suggests severe disease. Mild UC does not manifest fever, tachycardia, anemia, or elevated ESR levels; rather, these signs are indicative of severe UC. See exhibit A tab 2 (Truelove & Witts), at pdf 2. The only criteria not clearly met for severe UC is severe diarrhea (six or more motions a day) with macroscopic blood in stools. Moderately severe UC is defined as simply "Intermediate between severe and mild." Id. Dr. Santoro does not comment on the AGA criteria or provide any reference to other criteria in arguing Mr. Gapen's UC was well controlled. This lack of development reduces the persuasiveness of Dr. Santoro's opinion. See Nordwall v. Sec'y of Health & Hum. Servs., 83 Fed. Cl. 477, 488 (2008) ("The Court cannot fault the Special Master for relying on the opinion of one expert bolstered by medical literature over the unsupported opinion of another expert."). Thus, the undersigned finds that Mr. Gapen's condition is better characterized at this time as moderately severe UC.

b) The February 2016 colonoscopy supports a finding that Mr. Gapen's UC was moderately severe before vaccination.

To quickly address and manage a disease not fully diagnosed, on February 12, 2016, doctors prescribed a tapering dose of prednisone and referred Mr. Gapen to specialists. On February 22, 2016, Mr. Gapen was evaluated by Dr. Van Handel, a gastroenterologist. Mr. Gapen was assessed with colitis. Dr. Van Handel acknowledged the prednisone (corticosteroids) would negatively affect diagnostic confirmation and disease evaluation. In other words, the prednisone could mask symptoms. Thus, a colonoscopy was ordered for further evaluation. The February 25, 2016 colonoscopy revealed mild-moderately active chronic colitis consistent with UC, later described as panulcerative colitis.

The colonoscopy suggests Mr. Gapen's colon was in an active disease state, and it is strong evidence that Mr. Gapen's UC was also active in late February 2016. However, Dr. Santoro does not discuss the significance of this record in justifying his position. This omission too reduces the persuasiveness of his report.[31]

c) Improvements in symptoms reported in May 2016 were likely to be temporary.

Following the February 25, 2016 colonoscopy, Mr. Gapen continued taking the tapering doses of prednisone and was started (at some point prior to or contemporaneously with vaccination) on Lialda. That prednisone treatment concluded in late April 2016. The lack of medical records during this period (February 25 – May 24, 2016) suggests Mr. Gapen's symptoms were manageable and not severe enough to prompt hospitalization. However, when Mr. Gapen stopped taking prednisone in April of 2016, his UC was not cured. Without anti-inflammatory and immunosuppressive effects of prednisone (or another drug), Mr. Gapen's UC was likely to flare again. Exhibit C at 4. As Dr. Leonard noted, "it was about 6-8 weeks after going off the prednisone his bowels started to flare up and cause more diarrhea and bloody stools." Exhibit 7 at 3-4.

[31] The lack of other symptoms suggests Mr. Gapen's condition was improving from the December 2015 / January 2016 flare. Exhibit A at 10. These improvements are readily attributable to the prednisone treatment, which can improve inflammatory symptoms but would not treat the underlying disease. Id. at 9-10. These changes are also consistent with the "waxing and waning" course that many UC patients experience. Exhibit 31 at 10.

By May 24, 2016, Mr. Gapen's health appeared to be improving since his initial UC flare. Mr. Gapen's hemoglobin levels had risen from 9.0 g/dL to 10.3 g/dL. Exhibit 5 at 18-20. WBC and CRP levels were normalizing. He was not reporting abdominal pain or diarrhea and he had gained back twenty pounds of lost weight. Id. at 12.

However, petitioner's position that Mr. Gapen's UC was well controlled and in remission carries little weight. More likely, between late 2015 and February 2016, Mr. Gapen's UC was not well controlled and not in remission. Symptoms apparently resolved during the March to May 2016 timeframe, but this was likely the initial prednisone treatment managing the symptoms. Any remission would likely be temporary given the course of UC. Exhibit C at 3-4; see also exhibit 31 (Dr. Santoro explaining that IBD "has a waxing and waning course with asymptomatic remission period and with episodes of disease where patients present with symptoms, such as hematochezia, fever, and abdominal pain"). Furthermore, it remained uncertain whether Mr. Gapen would experience subsequent flares after transitioning off prednisone. The expected course of Mr. Gapen's UC would be "difficult to predict but would have included periods of remission and flare." Exhibit 31 at 11.

Although Mr. Gapen's UC was improving in May 2016, any apparent remission would likely be due to prednisone treatment. Endoscopic healing was not confirmed. Though improving, it is unclear whether Mr. Gapen was in clinical remission at the time of vaccination. See exhibit C tab 1 (Ha et al.), at pdf 2 (defining clinical remission as "an absence of corticosteroids and complete relief of colitis symptoms based on the physician's global assessment and patient report").

In sum, the undersigned finds that Mr. Gapen's condition prior to vaccination is best characterized as moderately severe ulcerative colitis. Furthermore, whether or not Mr. Gapen was in symptomatic remission (absent endoscopic healing) would not necessarily predict whether he would experience subsequent UC flares.

B. Did Mr. Gapen Suffer from a Serum Sickness Like Reaction?

When describing Mr. Gapen's condition following the vaccination, the parties view Mr. Gapen's medical records through competing lenses. Mr. Gapen's experts argue he experienced an SSLR adverse reaction to the PCV-13 vaccine.

His experts further argue the SSLR aggravated Mr. Gapen's underlying UC. The Secretary's experts disagree.[32]

The analysis of this issue considers (1) the pertinent medical records, (2) Mr. Gapen's interpretation of these records as indicating an SSLR, (3) the Secretary's arguments that an SSLR did not occur or aggravate Mr. Gapen's UC, and (4) the Secretary's arguments that Mr. Gapen's UC better explains his symptoms. Based upon these factors, a conclusion is reached in section (5) below.

1. Recitation of Pertinent Medical Records

Three days after the PCV-13 vaccination, on May 27, 2016, Mr. Gapen went to the emergency room. He reported that the day prior (May 26, 2016), he developed hives on legs and testicles (no hives on hands or feet). A photo demonstrates many circular red "coalescing lesions" on the inner thigh. Exhibit 19 at 3; exhibit 6 at 10. He had a fever, sore throat, and myalgias. Notably, neither diarrhea nor abdominal pain were reported. Treating doctors were uncertain whether the symptoms were related to the vaccination, sepsis, autoimmune disorder, or a viral syndrome. See exhibit 6 at 1-3, 10.

On May 28, 2016, Mr. Gapen was diagnosed by Dr. Worku with a drug reaction: EM related to PCV-13 vaccination. Exhibit 6 at 12; see also id. at 13-14 ("classic for erythema multiforme"). However, the parties agree that Mr. Gapen did not suffer EM. Upon discharge on May 29, 2016, most symptoms had resolved. Differential diagnoses were considered. Exhibit 6 at 23-24. Mr. Gapen continued taking Lialda. During a June 2, 2016 follow-up visit at Fairview Clinic, a treater noted "Serum sickness, subsequent encounter." Exhibit 4 at 62. No rashes were noted. Subsequent lab values on July 12, 2016 were acceptable and suggested improvement. Exhibit 5 at 21.

On August 4, 2016, Mr. Gapen saw Dr. Leonard for a rheumatology evaluation. Dr. Leonard felt Mr. Gapen's symptoms were "highly likely inflammatory arthritis and tendinitis associated with the colitis. . . . I don't think the inflammatory arthritis [is] secondary to the pneumonia vaccination." Exhibit 7 at 3-4.

[32] The parties ultimately agreed that Mr. Gapen did not have EM or SJS from the vaccination. Pet'r's Br. at 19; Resp't's Br. at 11.

Mr. Gapen had a follow-up appointment with Dr. Van Handel on September 6, 2016. Dr. Van Handel wrote Mr. Gapen had previously been diagnosed with SJS secondary to Prevnar vaccine. Exhibit 5 at 24. But, the parties agree Mr. Gapen did not have SJS. Daily prednisone treatment resumed and Humira was discussed. Exhibit 5 at 24-25. Colon biopsies on September 15, 2016 were suggestive of improvement, noting "mildly active chronic colitis." Id. at 34. Mr. Gapen also testified that he broke out in a painful rash in late September 2016. Exhibit 3 at 2-3. Then, on October 11, 2016, Mr. Gapen was started on Humira. He had been feeling better by this visit. Exhibit 5 at 38-39.

After starting Humira, Mr. Gapen's symptoms were better managed. Medical records were not generated between December 2016 and December 2017. Swelling was almost completely gone by March 2017 and flareups were milder. Exhibit 3 at 3. However, Mr. Gapen reported mental health issues that escalated in December 2017 and January 2018. Exhibit 3 at 3-5; exhibit 6 at 226; exhibit 4 at 74.

Dr. Ghattaura saw Mr. Gapen saw on February 13, 2018, noting: "He might have gotten serum sickness like reaction to Prevnar vaccine but those symptoms should not persist even a year later." Exhibit 10 at 4. Dr. Ghattaura prescribed Plaquenil. Exhibit 10 at 31-32. Near resolution of joint aches was reported on November 20, 2018.

A May 7, 2019 colonoscopy found mucosal healing throughout the colon with no inflammation. Exhibit 15 at 14. On June 3, 2019, Dr. Van Handel recorded Mr. Gapen's UC was "in clinical and endoscopic remission on Humira every 10-day dosing." Id. at 21.

2. Petitioner's Position Regarding SSLR

Mr. Gapen argues his medication was "working perfectly" at the time of vaccination. Pet'r's Br. at 7. Accordingly, he argues an SSLR best explains his hospitalization course and subsequent symptoms.

Mr. Gapen notes hives, fever, swellings, myalgias, and related symptoms prompted his hospitalization on May 27, 2016. He highlights the lack of GI symptoms and notes instances where treaters characterized his symptoms as a "drug reaction," "immune response," and "adverse reaction." Id.

Following the late May 2016 hospitalization, Mr. Gapen next notes swelling and joint aches periodically, prompting a visit to a rheumatology specialist on August 4, 2016 and Dr. Van Handel on September 6, 2016. Pet'r's Br. at 7-8. Then he discusses mental health problems in December 2017. The additional rashes and joint pains are mentioned in passing. Id. at 8-9.

Dr. Jacob provides a review of EM and SJS and explained why they are inapplicable diagnoses for Mr. Gapen's condition in late May 2016. See exhibit 19 at 6-9, 11-12. Instead, Dr. Jacob opines Mr. Gapen experienced a serum sickness-like reaction, which best explains Mr. Gapen's hospitalization course and subsequent symptoms. Exhibit 19 at 12; see also exhibit 45 at 4 (the "most likely explanation is that the pneumococcal vaccine was the immediate cause of his symptoms."). Dr. Santoro also endorsed this explanation as "very probable." Exhibit 31 at 9. According to Dr. Jacob, there was a "lack of any other notable changes in medication" that could explain the symptoms. Exhibit 45 at 3.

Dr. Jacob explains that SSLRs do not have universally accepted diagnostic criteria, though diagnosis often follows rash with hive-like lesions, fever, myalgias, and arthralgias occurring proximally to an exposure or inciting agent. Exhibit 19 at 10, 12. Drugs are the primary etiology. Id. at 10. Dr. Jacob provides medical literature that demonstrate SSLRs have been associated (albeit rarely) with pneumococcal and other vaccines. Id.; see exhibit 28 (Hengge et al. letter to editor); see also exhibit 29 (Chiong et al. case report). Dr. Jacob identifies Mr. Gapen's condition following vaccination as consistent with literature reports of SSLRs. Exhibit 19 at 11-12.

Dr. Jacob states serum sickness is an acute immune system reaction that occurs one to two weeks after exposure to a non-human protein. Exhibit 19 at 9. As he concedes, here, "the temporal relation between the potential exposure and the reaction is shorter than might be expected." Exhibit 19 at 12. However, "this would not exclude the diagnosis." Id. To address this issue, Dr. Jacob offers post-licensure safety surveillance which shows three VAERS reports of SSLRs within one day of pneumococcal conjugate vaccination. Exhibit 47 (Wise et al.), at pdf 1, 4. Dr. Jacob also notes serum sickness and SSLRs have been reported within a few days with other vaccines. Exhibits 48, 49, 50. Dr. Jacob also notes the "possibility" that Mr. Gapen had been previously sensitized to a constituent of

the vaccine.[33] However, this opinion rests on speculative grounds and is not persuasive without proof of a prior exposure to a specific protein.

Mr. Gapen emphasizes the abrupt development of symptoms previously unassociated with his UC, arguing this difference suggests an aggravation via SSLR. Pet'r's Br. at 12; exhibit 31 at 10; exhibit 45 at 3. However, Dr. Jacob concedes that SSLRs typically resolve on their own within a few days. To support the aggravation theory, he opines that here, in contrast, "a systemic inflammatory process related to an underlying chronic disease would typically require a more prolonged course of therapy for recovery." Id. at 4. Dr. Santoro states Mr. Gapen's "ongoing serum sickness like reaction . . . accounted for his exacerbation of ulcerative colitis." Exhibit 31 at 9.

3. Respondent's Position regarding SSLR

The Secretary argues the evidence does not support a finding that Mr. Gapen suffered an SSLR. Resp't's Br. at 11-18. The Secretary similarly argues Mr. Gapen has not explained how an SSLR could significantly aggravate UC. Id. at 18.

Dr. Maverakis concedes that SSLRs "are a well-documented adverse event of vaccination" but notes "they take time to develop." Exhibit A at 11. For support, he raises a case series of SSLR reports in health care providers following influenza vaccination, noting the median onset time was 9 days after receiving their second dose. Id.; exhibit A tab 6 (Apisarnthanarak et al.). As such, Dr. Maverakis opines that two days would be "an exceedingly short time to develop serum sickness" "[e]ven in patients who receive annual influenza vaccinations[.]" Exhibit A at 11. This is because "it takes considerable time for an antibody response to be mounted." Id. Thus, Dr. Maverakis argues the timing is not consistent with an SSLR because it would take more than two days for an antibody response to develop and form immune complexes. Exhibit A at 11.

Furthermore, the Secretary's experts note the chronicity of symptoms is not consistent with an SSLR. Dr. Longman plainly states: "There is no evidence to

[33] However, Dr. Jacob does not provide support that Mr. Gapen had prior sensitization to a vaccine component. Dr. Jacob speculates that Mr. Gapen may have had prior exposure to the conjugate protein of PCV-13 (a nontoxic variant of diphtheria toxin) through a routinely recommended conjugate meningococcal vaccine. Exhibit 45 at 2. But, no further support is provided.

suggest that the SSLR was ongoing as Dr. Santoro suggests." Exhibit C at 5. Dr. Maverakis (in agreement with Dr. Jacob) states SSLRs resolve within 2-6 days, often without any treatment. Exhibit A at 11; exhibit A tab 6 (Apisarnthanarak et al.); exhibit A tab 7 (Warrington et al.). Accordingly, Dr. Maverakis opines it is "virtually impossible for [Mr. Gapen] to have developed a chronic vaccine-associated serum sickness-like disease." Exhibit A at 11.

4. Respondent's Position regarding Alternative Explanation

The Secretary argues Mr. Gapen's post-vaccination clinical course is consistent with the expected clinical course of UC and that the vaccine was not a "substantial factor" in aggravating the UC. Respt's Br. at 27-28 (noting Sharpe prohibits a special master from "requiring petitioner 'to prove her expected outcome and that her post-vaccination condition is worse than this expected outcome.' 964 F.3d at 1082."), 33-34. As such, the Secretary argues Mr. Gapen's symptoms are best attributed to his UC.

Dr. Maverakis notes it is "extremely common" for UC patients to develop extraintestinal skin and joint manifestations. Exhibit A at 12. Dr. Longman concurs and argues that Mr. Gapen's hospitalization and associated joint symptoms are more likely explained by his underlying UC and IBD-associated arthritis. Exhibit C at 5. Noting Mr. Gapen's risk factors and that inadequate control with medicine is a major reason for flares, Dr. Longman opines that symptomatic remission alone was not proof of a healed colon. Id. at 3-4. For Dr. Longman, Mr. Gapen's symptoms coincide with onset of intestinal inflammation and persist until the inflammation is controlled. Id. at 6. In sum, the Secretary argues Mr. Gapen's condition after vaccination is consistent with the clinical course of waxing and waning UC, "especially after weaning off prednisone treatment" and starting "mesalamine monotherapy." Resp't's Br. at 32, 33.

5. Conclusions

For the reasons that follow, the undersigned is not persuaded that Mr. Gapen suffered an SSLR or that an SSLR can cause ongoing complications.

When it is biologically plausible that a vaccination could have caused an onset of a disease, evidence is still required to demonstrate the disease's onset is within the time which one would expect to see such onset. Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1356-58 (2006). For the sake of simplicity, the undersigned will assume a pneumococcal vaccine can cause an SSLR. This

assumption does not meaningfully affect the outcome of the case because even with this assumption, other aspects of Mr. Gapen's position that he suffered an SSLR remain unpersuasive.

The undersigned understands that serum sickness is a hypersensitivity reaction occurring after exposure to foreign antigens, in which immune complexes are formed, deposited in tissues, and then activated. Exhibit A tab 6 (Apisarnthanarak et al.), at pdf 1. As stated by Dr. Maverakis, these processes mean that development of SSLRs takes multiple days.

To address the early onset issue, Dr. Jacob speculated about prior exposures. Exhibit 45 at 2. As discussed above, Dr. Maverakis persuasively undermines this speculative argument.

Dr. Jacob also provided case reports involving multiple vaccines and rapid onset SSLRs, and a study looking at VAERS reports. In general, case reports provide little, if any, information helpful to determining causation because they present only a temporal sequence of events in which the vaccination preceded an adverse health event. See K.O. v. Sec'y of Health & Hum. Servs., No. 13-472V, 2016 WL 7634491, at *11-12 (Fed. Cl. Spec. Mstr. July 7, 2016) (discussing appellate precedent on case reports); see also Porter v. Sec'y of Health & Hum. Servs., No. 99-639V, 2008 WL 4483740, at *13 (Fed. Cl. Spec. Mstr. Oct. 2, 2008), set aside on other grounds by Rotoli v. Sec'y of Health & Hum. Servs., 89 Fed. Cl. 71 (2009), reinstated, 663 F.3d 1242, 1254 (Fed. Cir. 2012) (stating the "special master's decision reveals a thorough and careful evaluation of all of the evidence, including . . . reports and medical literature"); W.C. v. Sec'y of Health & Hum. Servs., No. 07-456V, 2011 WL 4537887, at *13 (Fed. Cl. Spec. Mstr. Feb. 22, 2011) ("[C]ase reports are generally weak evidence of causation because [they] cannot distinguish a temporal relationship from causal relationship."), mot. for rev. denied, 100 Fed. Cl. 440 (2011), aff'd, 704 F.3d 1352 (Fed. Cir. 2013).

Mr. Gapen developed a rash within two days of the PCV-13 vaccine. However, persuasive evidence shows that the biologic processes to develop a serum sickness-like reaction takes multiple days. Exhibit 48 (Bonds & Kelly article), at pdf 2; exhibit A tab 6 (Apisarnthanarak et al.), at pdf 1-3. Thus, the rapidity of onset tends to undermine the argument that Mr. Gapen suffered an SSLR in May 2016. See Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1352 (2008) (ruling that a special master was not arbitrary in finding that a condition occurred too quickly after a vaccination to have been caused by the vaccination).

A second reason for rejecting Mr. Gapen's claim that he suffered an SSLR is that the doctors who treated him did not concur on this diagnosis. The opinions of treating doctors can be quite probative. Cappizano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. See McCulloch v. Sec'y of Health & Hum. Servs., No. 09-293V, 2015 WL 3640610, at *20 (Fed. Cl. Spec. Mstr. May 22, 2015). However, the views of a treating doctor are not absolute, Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.67 (2009), even on the question of diagnosis, R.V. v. Sec'y of Health & Hum. Servs., 127 Fed. Cl. 136, 141 (2016), appeal dismissed, No. 16-2400 (Fed. Cir. Oct. 26. 2016). The views of treating physicians should also be weighed against other, contrary evidence present in the record—including conflicting opinions among such individuals. Hibbard v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 742, 749 (2011) (finding that it is not arbitrary or capricious for special masters to weigh competing treating physicians' conclusions against each other), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Veryzer v. Sec'y of Health & Hum. Servs., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), mot. for rev. denied, 100 Fed. Cl. 344, 356-57 (2011), aff'd without op., 475 Fed. App'x 765 (Fed. Cir. 2012).

Admittedly, the views of the treating doctors are a complicated topic because the doctors discussed conditions, such as Stevens-Johnson syndrome, that Mr. Gapen did not have. See, e.g., exhibit 5 at 24, 38, 46, 54 (Dr. Van Handel stating Mr. Gapen was diagnosed with SJS); exhibit 51 at 93 (PA-C McGuigan did "not suspect a recurrent or prolonged SJS"); exhibit 6 at 10 (Dr. Yazigi considering adverse reactions versus "sepsis/SIRS"); exhibit 6 at 14 (Dr. Worku assessing symptoms as "classic for erythema multiforme"); exhibit 6 at 23 (Dr. Thorsen noting Mr. Gapen "was seen by infectious disease, who felt that he had erythema multiforme and an acute immunological reaction to the pneumococcal vaccine"). See also Pet'r's Br. at 22-23; Pet'r's Rep. at 3-4. But, the parties argued that Mr. Gapen did not suffer EM or SJS. Pet'r's Br. at 19; exhibit 19 at 12; Resp't's Br. at 11; exhibit A at 11.

Nonetheless, some treaters considered the possibility of an SSLR. The strongest support for SSLR is found in statements by Kyle Olson, PA-C from the Fairview Clinic. After Mr. Gapen was discharged from the hospital and sought follow up care at the Fairview Clinic, Mr. Olson noted "Serum sickness,

subsequent encounter" during a follow-up visit. Exhibit 4 at 62 (June 2, 2016).[34] Mr. Olson carried that characterization forward during an August 27, 2016 follow-up. Exhibit 51 at 106 ("possible serum sickness-like reaction"). However, these statements from Mr. Olson are not persuasive because they are conclusory and in conflict with other treaters' assessments and the medical literature. Although these records are considered, given the facts of this case, they are not sufficiently persuasive evidence to establish Mr. Gapen suffered an SSLR. See Sanchez v. Sec'y of Health & Hum. Servs., 152 Fed. Cl. 782, 797, 804-05 (2021), appeal docketed, No. 2021-1866 (Fed. Cir. Apr. 21, 2021); Holmes v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 469, 487-89 (2014) (finding the special master did not abuse her discretion in evaluating and declining to give substantial weight to certain medical records).

Additional support for the claim that Mr. Gapen suffered an SSLR might come from Dr. Ghattaura. Dr. Ghattaura opined: "He might have gotten serum sickness like reaction to Prevnar vaccine but those symptoms should not persist even a year later." Exhibit 10 at 4 (On February 13, 2018). Dr. Ghattaura's statement carries little support because Dr. Ghattaura also seems to dismiss the idea that Mr. Gapen suffered a long-standing SSLR.

A third reason for not crediting the claim of an SSLR concerns its duration. Mr. Gapen's experts maintain that an SSLR caused chronic problems. Exhibit 19 at 12; exhibit 31 at 9, 12; but see exhibit 45 at 4 (Dr. Jacob stating: "The most likely explanation is that the pneumococcal vaccine was the *immediate* cause of his symptoms." (*emphasis* added)). But, this position is inconsistent with medical literature that states an SSLR would last only a few days or sometimes a few weeks. Exhibits 45 (Dr. Jacob's report), at 4; exhibit 49 (Chiong et al. case report), at pdf 3; exhibit A (Dr. Maverakis's report), at 11; exhibits A tab 6 (Apisarnthanarak et al.), at pdf 3-4; exhibit A tab 7 (Warrington et al.). The undersigned credits the Secretary's experts' opinions that an SSLR is not likely to be chronic.

For these reasons, the undersigned finds that Mr. Gapen has failed to establish, on a more likely than not basis, that he suffered an SSLR. Because the SSLR claim underpins Mr. Gapen's overall theory to explain how the PCV-13

[34] During an August 27, 2019 follow-up, in recounting Mr. Gapen's medical history, Mr. Olson wrote Mr. Gapen's symptoms were attributed "to possible serum sickness-like reaction". Exhibit 51 at 106.

vaccine aggravated his UC, additional analysis is not necessary. See Hibbard v. Sec'y of Health & Hum. Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012).

Nevertheless, the undersigned also finds that the Secretary has met his burden of establishing Mr. Gapen's worsening of symptoms in May 2016 was a result of his underlying severe UC and suboptimal management. The Secretary's experts were persuasive in establishing the factors that increase a person's risk for relapsing disease and flares and were persuasive in establishing that Mr. Gapen had many of these risk factors. Examples include: (1) UC diagnosis at a young age; (2) pancolitis at diagnosis; (3) severe endoscopic disease; (4) elevated CRP; (5) need for hospitalization; and (6) suboptimal control with medicine. See exhibit C at 3-4; exhibit C tab 1 (Ha et al.); exhibit C tab 2 (Rubin et al.).

C. Can a PCV-13 vaccination aggravate an underlying bowel disease via Molecular Mimicry?

Mr. Gapen also argues that molecular mimicry played a role in his health complications. Pet'r's Br. at 14-16, 18, 24. The Secretary disagrees. Resp't's Br. at 12-15, 19, 22.

Dr. Santoro put forward molecular mimicry as a potential mechanism. More specifically, he states the PCV-13 vaccine may have triggered an autoantibody against Mr. Gapen's intestinal epithelial cells. Exhibit 31 at 9. In part, Dr. Santoro relies on a case report of a patient developing histiocytic panniculitis following H1N1 vaccination. Exhibit 38 (Pauwels et al. case report). Additionally, Dr. Santoro references a report of flares of pre-existing IBD following HPV vaccination. Exhibit 40 (Jacobson et al.). Dr. Santoro opines that molecular mimicry may cause the exacerbation of IBD within one to twenty weeks after vaccination. Exhibit 31 at 10. Dr. Jacob did not discuss molecular mimicry in either of his two reports.

Dr. Longman does not agree that molecular mimicry played a role in this case. First, Dr. Longman critiques Dr. Santoro's reliance on the above case report because the disease discussed (panniculitis) is not relevant here. Exhibit C at 5. Furthermore, the authors of that report discuss thimerosal, not molecular mimicry, as a potential causative factor. Id.; see exhibit 38 at 219. Second, Dr. Longman argues the Jacobson article is inapplicable here because although the report notes two patients hospitalized with UC exacerbations, the investigators felt the

hospitalizations were due to active disease rather than vaccination. Exhibit C at 5-6; see exhibit 40 at 7.[35]

Dr. Longman's criticism of molecular mimicry as applied to this case is persuasive. Dr. Santoro does not thoroughly explain the basis for his opinion or his reliance on the Pauwels case report or Jacobson article. Dr. Santoro also stated that molecular mimicry could be the cause of illness between one and twenty weeks after vaccination. However, Mr. Gapen's condition seemed worse a few days after vaccination and he experienced subsequent improvement. Thus, it is unclear how molecular mimicry fits in Mr. Gapen's case. The lack of development reduces the value of Dr. Santoro's opinion. See Duncan v. Sec'y of Health & Hum. Servs., 153 Fed. Cl. 642, 661 (2021) (denying a motion for review and finding that the special master was not arbitrary in observing that the reports from petitioner's experts were conclusory); Harrington v. Sec'y of Health & Hum. Servs., 139 Fed. Cl. 465, 470 (2018) (denying a motion for review and indicating that there was no basis to disturb the special master's description of petitioner's expert opinion as "unpersuasive, conclusory, and disjointed").

Furthermore, the amended petition notes Mr. Gapen is pursuing a claim based on an SSLR and significant aggravation of his UC. Am. Pet., filed May 4, 2020, at 1. The theory that molecular mimicry was involved in the development of an alleged SSLR (or some separate aggravation of the UC) is undeveloped and perplexing. Pet'r's Br. at 14-16, 18, 24; Pet'r's Rep. at 2. As such, the undersigned does not find Dr. Santoro's molecular mimicry theory to be persuasive.

VI. Summary of the Special Master's Evaluation

After reviewing the record as a whole, the undersigned has found that Mr. Gapen's experts' views of the case were less persuasive than the Secretary's expert opinions. First, Mr. Gapen's position that he was in good health and well controlled on his medications prior to vaccination, as stated by Dr. Santoro, is not supported by the record. This faulty premise tends to undermine Mr. Gapen's presentation. The premise also misrepresents Mr. Gapen's health indicators post-vaccination. Second, although Dr. Jacob and Dr. Santoro discussed Mr. Gapen's medical history and supported their opinions, they fail to persuade the undersigned (a) that Mr. Gapen did in fact suffer an SSLR within 2 days after vaccination and

[35] However, the investigators also noted they "cannot definitely exclude a role for the vaccine in their hospitalizations."

(b) that an SSLR can chronically aggravate Mr. Gapen's underlying UC. Furthermore, on a more likely than not basis, it seems that SSLRs resolve within days, not months, and that Mr. Gapen has not persuasively explained how an SSLR could cause ongoing UC complications. Third, the undersigned also found Dr. Santoro's molecular mimicry theory to be unpersuasive, further weakening petitioner's position. By contrast, Dr. Maverakis's opinion is more persuasive. On a more likely than not basis, it seems Mr. Gapen experienced waxing and waning UC symptoms that varied based on evolving treatment protocols.

VII. Loving Analysis

The remaining step is to place these findings into the framework for analysis set out by Loving. A special master may evaluate the Althen factors, which correspond to Loving factors 4-6, without first considering the first three Loving factors. Paluck v. Sec'y of Health & Hum. Servs., 104 Fed. Cl. 457, 469 (2012), aff'd after intervening remand, 786 F.3d 1373 (Fed. Cir. 2015).

Here, as set forth above, Mr. Gapen has failed to meet his burden of proof on two aspects of his claim: a medical theory causally connecting the worsening of his symptoms to the vaccination and a logical sequence of cause and effect. In addition, the Secretary has met his burden of proof on another aspect, that Mr. Gapen's deterioration was due to his pre-existing UC.

A. A Medical Theory Causally Connecting A Significantly Worsened Condition To The Vaccination

The undersigned understands the fourth prong of the Loving test (the first prong of Althen) is to present the general question of whether a particular vaccine (here, pneumococcal conjugate vaccine) can significantly aggravate a particular condition (here, ulcerative colitis). Mr. Gapen's experts have raised molecular mimicry and SSLR as medical theories causally connecting his allegedly aggravated condition to the pneumococcal vaccine.

However, as set forth in section V.C above, Mr. Gapen has not demonstrated how molecular mimicry is a persuasive theory to explain how a pneumococcal conjugate vaccine can worsen UC. Thus, Mr. Gapen is not entitled to compensation.

B. A Logical Sequence Of Cause And Effect Showing That The Vaccination Was The Reason For The Significant Aggravation

The fifth prong of the Loving test (the second prong from Althen) requires petitioner to show a logical sequence of cause and effect showing that the vaccine was the reason for his condition's significant aggravation. A logical presentation would entail showing that petitioner's reaction to the pneumococcal conjugate vaccine was consistent with the theories articulated by his experts. See Hibbard v. Sec'y of Health & Hum. Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012); Dodd v. Sec'y of Health & Hum. Servs., 114 Fed. Cl. 43, 52-57 (2013); La Londe v. Sec'y of Health & Hum. Servs., 110 Fed. Cl. 184, 205 (2013), aff'd, 746 F.3d 1334 (Fed. Cir. 2014).

As an indirect method by which the pneumococcal vaccine could aggravate Mr. Gapen's UC, Mr. Gapen also presented SSLR. However, as explained in section V.B.5, above, the development of a rash within 2-3 days of the vaccination makes the development of an SSLR unlikely. Furthermore, the experts agree that SSLRs typically resolve within days, yet Mr. Gapen has not cited any literature explaining how an SSLR could cause ongoing complications or worsen Mr. Gapen's UC. See Resp't's Br. at 15-16. Thus, the sequence of events propounded by Dr. Jacob is not logical.

C. Contribution, If Any, of Pre-existing Problem

In evaluating a significant aggravation case, special masters may consider how the underlying pre-existing disease affected the person's health. Locane, 685 F.3d at 1381; Loving, 86 Fed. Cl. at 144 (placing burden on respondent after petitioners "successfully put forward such a prima facie case"); Gruber v. Sec'y of Health & Hum. Servs., 61 Fed. Cl. 674, 684 (2004) (discussing significant aggravation in the context of an on-Table claim). The Secretary bears the burden on this issue after a petitioner presents a prima facie case. Sharpe, 964 F.3d at 1081.

Here, for the reasons explained in section V.B.5 above, the Secretary has established that Mr. Gapen's course is more likely to be the result of his active waxing and waning UC. Stated differently, the pneumococcal vaccination was not a significant factor in Mr. Gapen's changed health in and following May 2016.

This is an additional and separate reason for finding that Mr. Gapen is not entitled to compensation.[36]

D. Remaining Loving Factors

Given the findings above, an evaluation of the other factors from the Loving test is not required.

VIII. A Disposition on the Papers is Appropriate

Mr. Gapen has requested a ruling on the record. Pet'r's Mot., filed July 26, 2021, at 1. While the parties' views are entitled to some consideration, they do not determine whether a hearing will be conducted. Congress authorized and the Vaccine Rules indicate special masters to have discretion in determining whether to hold a hearing. Kreizenbeck v. Sec'y of Health & Hum. Servs., 945 F.3d 1362, 1365 (Fed. Cir. 2020).

A hearing is not required to adjudicate Mr. Gapen's case. The parties have filed reports from the doctors whom they retained, and petitioner filed the last expert report. The parties have also submitted briefs and petitioner filed the last brief. Under these circumstances, Mr. Gapen has enjoyed a full and fair opportunity to present any evidence and argument he wished.

IX. Conclusion

For the above stated reasons, Mr. Gapen has not demonstrated the PCV-13 vaccine caused him to suffer an SSLR and subsequent significant aggravation of his underlying UC. Accordingly, the Clerk's Office is instructed to enter judgment against Mr. Gapen unless a motion for review is filed. Information for filing a motion for review, including the deadline by which any such motion must be filed, is available on the website of the Court of Federal Claims.

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[36] Furthermore, this finding seems to preclude petitioner's 6-month severity requirement. 42 U.S.C. § 300aa—11(c)(1)(D). C.f. Snyder v. Sec'y of Health & Hum. Servs., No. 07-59V, 2011 WL 3022544, *35-36 (Fed. Cl. Spec. Mstr. May 27, 2011) (finding evidence did not support that child's fever immediately after vaccination, which triggered a seizure, caused an injury lasting more than six months), rev'd, 102 Fed. Cl. 305 (2011), reinstated on other grounds, 553 Fed. Appx. 994 (Fed. Cir. 2014).

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master