In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 13-439V
(to be published)

CAROLYNNE OLSON,	*	
	*	Filed: July 14, 2017
Petitioner,	*	
v.	*	Decision; Dismissal of Claim; Human Papillomavirus ("HPV") Vaccine; Rheumatoid Arthritis ("RA"); Causation Theory; Alum Adjuvant; Cytokine Upregulation.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Mitchel J. Olson, Law Office of Mitchel J. Olson, JD, MD, Carlsbad, CA, for Petitioner.

Jennifer L. Reynaud, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On July 1, 2013, Carolynne Olson filed this action seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program"[2]). Petition ("Pet.") (ECF No. 1). Petitioner alleges that she developed rheumatoid arthritis ("RA") as a result of the human papillomavirus ("HPV") vaccine she received on July 1, 2010. Pet. at 1. An entitlement hearing was held in Washington, DC, on March 27-28, 2017.

[1] This decision will be posted on the United States Court of Federal Claims' website, and in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the ruling will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire decision will be available in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. § 300aa-10 through 34 (2012)) (hereinafter "Vaccine Act" or "the Act"). All subsequent references to sections of the Vaccine Act shall be to the pertinent subparagraph of 42 U.S.C. § 300aa.

Many facts relevant to Petitioner's claim are undisputed or unrebutted: she has been diagnosed with RA, and her obvious clinical symptoms manifested not long after she received the HPV vaccine. The primary issue to be resolved is whether Petitioner's causation theory is reliable and persuasive. After considering the record as a whole, and for the reasons explained below, I find that Petitioner has failed to carry her burden in establishing causation, and therefore her request for entitlement is **DENIED**. Petitioner's causation theory is wholly dependent on the vaccine's adjuvant causing her RA, but reliable science does not corroborate its alleged potential to initiate a pathogenic sequence. Moreover, Petitioner's medical history does not demonstrate her theory in action.

I. Factual Background

Petitioner received a Gardasil vaccination from her gynecologist, Angelica Zaid, M.D., on July 1, 2010. Ex. 1 at 11. At the time of vaccination, she was 52 years old, and therefore (as discussed further below) not within the target age group to receive the vaccine. However, as the administration note stated, she asked to receive it nonetheless after learning from her daughter's dermatologist that the vaccine could be effective in treating warts. *Id.*; Tr. at 4.

Mrs. Olson's medical history as of the date of her vaccination was significant for hypothyroidism, vitamin D deficiency, osteochondroma,[3] an Achilles tendon rupture, and anemia. Ex. 2 at 1. She had additionally seen her otolaryngologist ("ENT") specialist, Cynthia Davis, M.D., from 2007 to 2009 for sinus-related symptoms, and she was diagnosed with chronic sinusitis in September 2008. Ex. 4-1 at 13. Petitioner also testified that she suffered generally from asthma since childhood. Tr. at 9. Petitioner's chronic respiratory problems are highly relevant to her causation theory.

Immediate Post-Vaccination Health

The medical records from the months immediately following Mrs. Olson's receipt of the HPV vaccine do not set forth any occasions when she complained of RA-like symptoms. Thus, nearly three months after receiving the Gardasil vaccine, on September 24, 2010, Petitioner saw Dr. Davis with complaints of sinus pressure, facial pain, and lung congestion over the previous month. Petitioner at this time appears to have been diagnosed with acute sinusitis and reactive airway disease ("RAD"), and she was prescribed several medications, including prednisone and antibiotics. Ex. 4-1 at 35.

Nearly three more months passed before Mrs. Olson again visited a doctor. On December 13, 2010, Petitioner returned to Dr. Zaid for a hormone replacement therapy consult. The records

[3] Osteochondroma is a benign tumor consisting of projecting adult bone capped by cartilage projecting from the lateral contours of endochondral bones. *Dorland's Medical Dictionary* 1345 (32nd ed. 2012) (hereinafter *Dorland's*).

from this visit contain the first reference to any symptoms that could be associated with Petitioner's RA, noting that she reported to Dr. Zaid that she had developed "knuckle enlargement w[ith] pain (first R[ight] and then L[eft]) and persistent," after receiving the HPV vaccine. Ex. 1 at 12. Petitioner was assessed as having a vitamin D deficiency and hormone imbalance. *Id*. Dr. Zaid started Petitioner on estrogen replacement therapy, but also referred her to a rheumatologist, Alexander Shikhman, M.D., for evaluation of her knuckle enlargement and pain. *Id.*

2011-12 Treatment of Respiratory and Arthritic Symptoms

Petitioner returned to Dr. Zaid on January 13, 2011, complaining of pelvic pain, and she was diagnosed with bacterial vaginosis. Ex. 1 at 14-15. Dr. Zaid did not evaluate Petitioner for her joint symptoms, but instead reiterated her prior recommendation that she "see Dr. Shikhman" in January. *Id.* at 15. That appointment with Dr. Shikhman did not occur, however, until February 22, 2011. Ex. 2 at 33.

At her first visit to Dr. Shikhman, Mrs. Olson reported that she had received the HPV vaccine as therapy treatment for warts six months before and "soon after" began to experience symptoms (pain, knuckle enlargement, fatigue, etc.). Ex. 2 at 33. Such symptoms had become progressively worse, although she had noticed improvement after taking prednisone for a recent asthma attack. *Id*. Examination revealed confluent erythema of the hands, dermatitis herpetiformis-like lesions over her elbows, low grade synovitis of her proximal interphalangeal joints ("PIPs") and metatarsophalangeal joints ("MTPs"), and tenderness of her elbows, wrists, knees, and ankles. *Id*. at 34. A musculoskeletal ultrasound showed small effusion with synovial hypertrophy of both knees, low grade synovitis of the left wrist extensor tendon sheaths, a small right wrist effusion with active synovitis of the extensor tendon sheaths, and active bicipital tenosynovitis of both shoulders with periarticular calcific deposits. *Id.*

Dr. Shikhman's records from his initial visit with Mrs. Olson noted that her "clinical presentation [wa]s highly suspicious for reactive arthritis." Ex. 2 at 34. He proposed the existence of an evolving inflammatory arthropathy or a crystal-induced arthropathy.[4] *Id*. Other possible etiologies included in the differential diagnoses were knee enthesopathy,[5] carpal tunnel syndrome, and rotator cuff syndrome. *Id*. Dr. Shikhman noted a history of Raynaud's disease[6] for Mrs. Olson,

[4] Arthropathy includes any joint disease. *Dorland's* at 158. Crystal-induced arthropathy is arthritis due to the deposition of inorganic crystalline material within the joints. *Id.* at 150.

[5] Enthesopathy is a disorder of the muscular or tendinous attachment to the bone. *Dorland's* at 627.

[6] Raynaud's disease is a primary or idiopathic vascular disorder characterized by areas of the body (such as fingers or toes) feeling numb in response to cold temperatures or stress due to limited blood circulation to affected areas. *Dorland's* at 542; *Diseases and Conditions: Raynaud's Disease*, The Mayo Clinic, http://www mayoclinic.org/diseases-conditions/raynauds-disease/basics/definition/CON-20022916 (last visited Jul. 5, 2017). It affects females more often than males. *Dorland's* at 542.

and he was of the opinion that gluten intolerance and connective tissue disease should be ruled out. *Id*.

During the February 2011 visit to Dr. Shikhman, Petitioner had extensive laboratory testing performed. Ex. 2 at 101-02, 104, 106-09, 111. Results showed a mildly elevated sedimentation rate, as well as a positive Mycoplasma IgG antibody level – indicative of a prior resolved infection. *Id.* at 101, 109, 111. Other test results were normal, including C-reactive protein levels, rheumatoid factor, autoimmune panel, celiac disease, and Chlamydia pneumonia. *Id.* at 101-02, 104, 106-09. Importantly, this initial testing did not reveal the presence of anti-citrullinated protein antibodies ("ACPA") – a biomarker strongly associated with RA and relevant to Petitioner's claim, as discussed in greater detail below.

Mrs. Olson had a follow-up visit to Dr. Shikhman the next month, on March 29, 2011. At this time, additional testing was performed, and the lab results now showed low IgG levels, elevated sedimentation rate, and mild anemia, along with low thyroid hormone levels. Ex. 2 at 31. Petitioner's physical exam was otherwise consistent with her February exam, but Dr. Shikhman added hypothyroidism to his previous diagnoses. *Id.* at 32.

While being treated for her arthritis symptoms in 2011, Mrs. Olson continued to experience the lung and respiratory conditions that predated her vaccination. Thus, on April 12, 2011, Petitioner returned to her ENT specialist, Dr. Davis, complaining of increased facial swelling, nasal discharge, and lung congestion. A nasal endoscopy performed at this time revealed results consistent with allergic rhinitis, but a CT scan of her chest performed the following week was negative for any acute disease. Ex. 4-1 at 47, 51, 53. Dr. Davis subsequently increased Mrs. Olson's prednisone dosage as her symptoms had not improved. *Id*. at 56. Two days later, on April 14, 2011, Petitioner consulted with a pulmonologist, W. Wayne Hooper, M.D., about a cough and a concern for lung infection. Ex. 8 at 26.

Petitioner saw Dr. Shikhman again on May 10, 2011. At this time, she informed him of the problems she had been having with bronchitis, but the record makes no mention of new complaints concerning her joints or previously-documented arthritic symptoms. Ex. 2 at 29-31. Repeat tests for mycoplasma showed a negative IgG and IgM. Ex. 2 at 100. Dr. Shikhman's notes and diagnoses remained unchanged from the March 29th visit. *Id.* However, Petitioner represented to other treaters that the cause of her arthritis-related symptoms was better understood than what Dr. Shikhman's records actually suggest. Thus, at a visit to Dr. Hooper on August 9, 2011, Mrs. Olson reported that she suffered from "joint disease involving her knuckles of both hands," which she described as attributable to "post inoculation [sic] arthritis from a wart infection on her body." Ex. 8 at 16.

Petitioner saw Dr. Shikhman on several occasions from September 2011 to December 2011 for her joint pain and concurrent symptoms, as well as shortness of breath, pain in her lungs, and fatigue. Ex. 2 at 19-23, 26. After a September visit, Dr. Shikhman listed several possible diagnoses: a clinical presentation highly suspicious for reactive arthritis; evolving inflammatory arthropathy versus crystal-induced arthropathy; chronic bronchitis; knee enthesopathy; carpal tunnel syndrome; rotator cuff syndrome; hypothyroidism; Raynaud's disease; and connective tissue disease. *Id*. at 28.

2012 Treatment

In 2012, Mrs. Olson continued to obtain treatment for both her respiratory and arthritis-related symptoms. With respect to the former, she went back to see Dr. Davis in January 2012, complaining of a headache, chest pain, and eye pain. Ex. 4-2 at 99. She had a productive cough and sinus drainage for which she received IVIG infusions for gamma globulin deficiency. *Id*. Dr. Davis noted diagnoses of asthma, allergic rhinitis, and chronic ethmoid sinusitis. *Id*. at 101. Petitioner followed up with Dr. Davis in June, but now reported that her symptoms had improved and that she was able to exercise regularly as well. *Id*. at 93, 101. Dr. Davis observed no joint swelling, and her differential diagnosis was consistent with prior diagnoses. *Id.* at 93, 95.

For treatment of her joint pain and swelling, Petitioner continued to see Dr. Shikhman. She returned to him in May 2012, complaining of worsening fatigue, hand stiffness, hand and calf weakness, and morning stiffness. Ex. 2 at 17. An examination confirmed the existence of "worsening of ulnar deviation" in Petitioner's right and left knuckles, with low grade synovitis of her hands and feet. *Id*. at 18. By the following month, however, Mrs. Olson reported to Dr. Shikhman that she felt much better. *Id.* at 13. Dr. Shikhman added "hypogammaglobulinemia vs. CVID [common variable immunodeficiency]" to his list of diagnoses. *Id*. at 13-14. At a final 2012 visit on December 28th, Dr. Shikhman recorded Petitioner's complaints of generalized hand pain. Ex. 2 at 5. Dr. Shikhman's diagnoses were unchanged from previous visits, however. *Id*. at 6-7.

Treatment by Dr. Middleton and RA Diagnosis

Mrs. Olson continued to experience in 2013 the same kinds of arthritis-related symptoms she claims to have first suffered around the time of her 2010 HPV vaccination, and to seek evaluation of these symptoms, although she was able to cope with them while leading an active life. *See, e.g.,* Ex. 8 at 6 (February 12, 2013, visit with Dr. Hooper); Tr. at 23, 25. During a June 11, 2013, visit to Dr. Shikhman, Petitioner was in fact noted to be doing well overall, reporting only "minor joint pain" which was controlled with a combination of herbs and supplements. Ex. 2 at 1.

By the late summer and early fall, however, Petitioner was finding coping with her pain more challenging – and treaters began to make more definitive diagnoses for her ongoing condition. Thus, on August 8, 2013, Petitioner saw Dr. Hooper for a routine examination. He now observed that her "hands [were] more arthritic" and that the "patient thinks it is related to a vaccination for warts." Ex. 8 at 1. By this point, the Petition had already been filed.

The next month, on September 10, 2013, Petitioner saw Gregory Middleton, M.D., a rheumatologist, for evaluation of "hand deformity." Ex. 5 at 171. At this first visit (now three years post-vaccination), Mrs. Olson informed Dr. Middleton that she had developed swelling of her knuckles in both hands about three months after receiving a Gardasil vaccination and that she had never noticed significant pain from it, but that she had a high pain tolerance that helped her to endure it. *Id*. She also observed that her pain was more manageable during the times she was taking prednisone for her respiratory symptoms, but that her arthritis symptoms became "a lot worse with both pain and swelling" when she was tapered off steroidal treatment. *Id.*

Dr. Middleton noted that although Petitioner had been seeing Dr. Shikhman throughout the entire period, she had never received formal treatment for arthritis. Ex. 5 at 1. Dr. Middleton's examination revealed mild Raynaud's changes in Petitioner's feet and reducible ulnar deviations of her knuckle joints, but no evidence of synovitis in the hands, wrists, elbows, knees, ankles or toes. *Id*. He diagnosed her with probable "seronegative" rheumatoid arthritis (meaning that testing did not reveal the presence of autoantibodies highly associated with RA, such as ACPAs or rheumatoid factor) attributable to "immune system over-reaction" from her 2010 HPV vaccine, although this record provided no explanation as to the basis for this conclusion. *Id.* at 2.

On September 16, 2013, Mrs. Olson saw Dr. Middleton again. Ex. 5 at 4. He noted that x-rays of her hand taken the previous week showed no evidence of bone erosions. *Id.* He felt that she had chronic inflammatory synovitis of her MTP joints "after Gardasil vaccination," which led to ulnar deviation without bone destruction, and he deemed her overall presentation in light of the exam to be "consistent with seronegative rheumatoid arthritis." He prescribed medication while also adding hypothyroidism and IgG deficiency/bronchiectasis to the differential diagnoses. *Id*. at 4-5.

Petitioner followed-up with Dr. Middleton on October 22, 2013, stating that her joint pain and function of her hands and feet had improved since she had begun taking medicines targeted for her RA. Ex. 5 at 6. Upon examination, she displayed mild active synovitis of the right MTP joint not present on her prior visits. *Id*. Dr. Middleton diagnosed mild but deforming seronegative inflammatory arthritis compatible with rheumatoid arthritis. *Id.*

Since then, Petitioner has continued to obtain treatment from Dr. Middleton. Tr. at 32. She has also repeated to other treaters her allegation in this action that her arthritic symptoms began

not long after she received the HPV vaccine, as well as her belief that the vaccine caused those symptoms. *See, e.g.,* Ex. 6-1 at 18 (onset/duration stated "6/2010 [sic] after Gardasil vaccine," with further notes that Petitioner "got a Gardasil vaccine to get rid of warts and then a month later got pain in hands and then 6 months later she got lots of problems").

II. RA and its Pathophysiology

Before reviewing the testimony offered at hearing regarding Petitioner's claimed injury and the role the HPV vaccine is alleged to have played, it would be useful to summarize the features of RA as well as its understood pathophysiology.

RA is a long-term autoimmune condition mainly affecting the joints. *See, e.g.,* M. van de Sande et al., *Different Stages of Rheumatoid Arthritis: Features of the Synovium in the Preclinical Phase*, 70 Ann. Rheum. Dis. 772-77 (2011) (filed as Article 3) ("van de Sande"). Its causes are thought to be a mix of immune, genetic, and environmental factors, but in essence it involves an autoimmune attack on the synovial membranes of the joints, causing inflammation and later erosion and destruction of joint surfaces, along with deformity of affected joints, fingers, or toes. *Id.* at 772. It can also cause complications in the lungs, kidneys, and other organs. *See, e.g.,* A. Ytterberg et al., *Shared Immunological Targets in the Lungs and Joints of Patients with Rheumatoid Arthritis: Identification and Validation*, 74 Ann. Rheum. Dis. 1772-77 (2015) (filed as Article 13) ("Ytterberg"); T. Skare et al., *Pulmonary Changes on High-Resolution Computed Tomography of Patients with Rheumatoid Arthritis and their Association with Clinical, Demographic, Serological and Therapeutic Variables*, 51 Rev. Bras. Reumatol. 4:325-37 (2011) (filed as Article 28).

RA initiates from some kind of nonspecific inflammatory event, the trigger for which can be a variety of things. G. Firestein, *Etiology and Pathogenesis of Rheumatoid Arthritis*, Textbook of Rheum. 1059-60 (10th ed. 2012) (filed as Article 1) ("Firestein"). But it is the subsequent stages of the condition where its pathologic amplification occurs – and where the autoimmune character of the condition manifests. *See, e.g.,* V. M. Holers, *Insights from Populations At-Risk for the Future Development of Classified Rheumatoid Arthritis*, 40 Rheum. Dis. Clin. North Am. 4:605-20 (2014) (filed as Article 21). Medical and scientific research has helped pinpoint one explanation for RA. Although not fully understood, it is now believed that some individuals, through a post-translational (or enzymatic) modification of certain amino acids found in the body, undergo "citrullination" – the conversion of the amino acid arginine into citrulline (not one of "the standard 20 amino acids encoded by DNA in the genetic code"). *See* N. Sofat et al., *Interaction Between Extracellular Matrix Molecules and Microbial Pathogens: Evidence for the Missing Link in Autoimmunity with Rheumatoid Arthritis as a Disease Model,* 5 Frontiers in Microbiology 1-6

(2015) (filed as Article 11[7]) ("Sofat"); Ytterberg at 1772. The adaptive immune system in such individuals will then create autoantibodies that attack the citrullinated proteins as if they were foreign antigens, and in the process encourage the autoimmune process and chronic inflammation that characterizes RA. Sofat at 1-2. This in turn leads to the progressive tissue damage that later causes the appearance of the more overt clinical signs of RA. *Id.*

There are a number of risk factors associated with the development of RA – some, but not all of which, are present in this case. Smoking is the most widely-recognized non-genetic risk factor, but it is inapplicable here as Mrs. Olson has not been established to be a smoker. *See* Ytterberg at 1; Sofat at 1-2; Tr. at 149-50. Gender, however, is another well-recognized risk factor, as more women than men develop the disorder. *See, e.g.,* V. Holers, *Autoimmunity to Citrullinated Proteins and the Initiation of Rheumatoid Arthritis*, 25 Curr. Opin. Immunol. 728:728 (2013) (filed as Article 22) ("Holers II"). Genetic factors are also associated with RA, but they have not been demonstrated to be applicable herein. Firestein at 1059; Holers II at 728. It is also undisputed in this case that Mrs. Olson has never been shown to possess two of the autoantibody biomarkers strongly associated with RA – rheumatoid factor or ACPAs – and this absence of evidence has some bearing on the persuasive strength of Petitioner's case, as discussed below.

III. Hearing Testimony

A. Petitioner's Witnesses

1. *Carolynne Olson* – Petitioner was the first witness to testify in the case. Her educational background includes a nursing degree, and she later practiced nursing. Tr. at 4. Petitioner confirmed her receipt of the HPV vaccine in July 2010, as well as the purpose of receiving it: to treat warts on her feet (since her daughter's dermatologist had informed her that the vaccine had this side effect). *Id.*

Importantly, Mrs. Olson maintained that she began to experience relevant symptoms ("burning in both hands") within one to two weeks of receipt of the vaccine (Tr. at 6), with "knobs" (or evidence of swelling) beginning to appear on her right hand knuckles about two to three months after July 1st. *Id.* at 6-7. She did not, however, seek treatment immediately, but waited for nearly six months – and in fact first informed her gynecologist, Dr. Zaid, about her condition rather than a rheumatologist. Tr. at 7-8.[8] She explained the delay as the product of her initial assumption that

[7] Petitioner's appendix of medical literature indicates this article as "Article 12" in the Volume 1 table of contents. However, the actual article within the appendix was marked as "Article 11."

[8] Mrs. Olson was asked about some medical records (particularly from her first visit to Dr. Middleton) suggesting that her symptoms actually began three months after the vaccination rather than two weeks. Tr. at 25. However, she maintained that her pain had been progressive in its severity, and therefore she had distinguished the degree of pain she felt shortly after receipt of the vaccine from what she experienced later on – consistent with her overall decision to delay medical treatment. *Id.*

her pain might resolve on its own (*Id.* at 8), noting as well that she was used to working through pain and discomfort due to her lifelong asthma (*Id.* at 9). *Id.* at 23.

2. *Dr. Gregory Middleton* – Dr. Middleton, one of Mrs. Olson's treaters, provided an opinion for the theoretical causative role the HPV vaccine could play in Petitioner's RA. In addition to testifying at hearing, Dr. Middleton provided three expert reports (presented in the form of witness affidavits) during the course of this matter. *See* Affidavit, dated December 1, 2014 (ECF No. 32) ("First Middleton Rep."); Supplemental Affidavit, dated December 1, 2015 (ECF No. 41) ("Second Middleton Rep."); and Second Supplemental Affidavit, dated January 14, 2017 (ECF No. 49-1) ("Third Middleton Rep.").

As reflected in his affidavit and trial testimony, Dr. Middleton is a clinical rheumatologist whose expertise primarily arises from his training and subsequent treatment of hundreds of patients. Tr. at 29-31. Dr. Middleton received his M.D. from Boston University in 1989, and he thereafter completed a residency in internal medicine in 1992 and a fellowship in rheumatology in 1994 at the University of Texas Southwestern. First Middleton Rep. at 1. He is board certified in rheumatology, and he serves as a clinical professor at the University of California San Diego Medical School in the rheumatology and orthopedics departments. *Id.* By his own admission, Dr. Middleton lacks deep or focused expertise in vaccines, nor is immunology his specialty (Tr. at 100 ("I am testifying here as a clinical immunologist, not as a vaccine expert")) – although in this case he repeatedly opined on matters in this case having far more to do with the immunologic process (or the literature offered to explain it)[9] than RA itself.

Dr. Middleton's first report sets forth a somewhat conclusory overview of Mrs. Olson's causation theory. After a brief recounting of Petitioner's medical history, Dr. Middleton opines that the HPV vaccine was likely causative of Petitioner's RA, deeming it an "auto-immune response triggered by the vaccination itself." First Middleton Rep. at 4. He placed heavy emphasis on the temporal relationship between receipt of the vaccine in 2010 and Petitioner's first symptoms approximately two weeks later, based upon reports contained in the records that Mrs. Olson made to treaters prior to the time that he began treating her. *Id*. at 2-3. He also relied on the vaccine's

[9] Petitioner's counsel led Dr. Middleton through a redirect examination in which the witness was largely asked to confirm or accept what various pieces of Petitioner's filed medical literature said on a specific issue, rather than to explain how the literature informed his opinion, based upon his demonstrated expertise in treating patients with RA. *See, e.g.,* Tr. at 88 ("going over to the second column of page 1065, the last sentence, 'Although the role of the inflammasome in RA has not been fully defined, its ability to induce cytokine production by exposure to bacterial products and other danger signals suggests that it is – that it participates in IL-1 and IL-18 regulation.' Do you agree with that statement?"). Petitioners may of course file medical and scientific literature supporting their claim independent of whether their expert selected it, or even specifically relies on it for his opinion (and special masters must review and consider that literature in ruling on entitlement). But factual statements contained in that literature do not become more probative simply because a witness confirms orally what the item already says – especially when that witness lacks sufficient particularized expertise in the subject matter of the underlying article to comment intelligently on the topic.

package inserts (which identified "arthralgia" as a known side-effect), as well as 43 instances of reports to the Vaccine Adverse Events Reporting System ("VAERS").[10] *Id.* at 5-6.

Dr. Middleton's second expert report endeavored to provide a more detailed scientific and medical explanation for potential causes of RA generally, as well as Petitioner's theory for how the HPV vaccine might have been involved in causing her RA specifically. He began with a discussion of Petitioner's current condition, acknowledging that she lacked the autoantibody biomarkers closely associated with RA – in particular the rheumatoid factor or the ACPAs – but that her diagnosis was still clinically correct due to the number of affected joints as well as the duration of her condition. Second Middleton Rep. at 2. Dr. Middleton otherwise downplayed the absence of these biomarkers, noting that 30 percent of RA patients lack them (Second Middleton Rep. at 3) – but in so doing implicitly acknowledged that the majority *do* possess them. He also stated that known genetic risk factors were more applicable to individuals positive for these antibodies, although some studies[11] established that even RA patients negative for ACPAs had enough genetic risk factors to develop the condition. *Id.* at 4.

Despite Mrs. Olson not possessing the more well-understood biomarkers or genetic factors that could explain her RA, Dr. Middleton opined that she did possess an important risk factor – her recurrent respiratory problems – that made her predisposed to develop RA under the right circumstances. Second Middleton Rep. at 5. Dr. Middleton noted that Petitioner was a lifelong asthma sufferer, and she had also been diagnosed with bronchiectasis, an "abnormal and permanent distortion of a bronchus or other airway . . . typically caused by a lung infection." Second Middleton Rep. at 7.[12] Citing several items of literature, he opined that current scientific and

[10] VAERS is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention and the Food and Drug Administration, and allows individuals who believe they may have experienced a vaccine reaction to make a report of the incident. *See* https://vaers hhs.gov/index (last visited July 6, 2017). Because it is a passive reporting system, VAERS database findings that a number of individuals have complained of a supposed adverse effect from a particular vaccine do not *imply* causation, although such evidence may suggest potential signals of causation. For this reason, special masters do not typically afford great weight to VAERS data in determining causation. *See Analla v. Sec'y of Health & Human Servs.,* 70 Fed. Cl. 552, 558 (2006) ("the Court [of Federal Claims] uniformly has upheld the Chief Special Master's concerns about the reliability of VAERS data") (*citations omitted*).

[11] For this proposition, Dr. Middleton cited an unfiled item of literature – T. Frisell et al., *Familial Risks and Heritability of Rheumatoid Arthritis: The Role of Rheumatoid Factor/Anti-Citrullinated Protein Antibody Status, Number and Type of Affected Relatives, Sex, and Age,* 65 Arthritis Rheum. 2773:2773-82 (2013). This was a consistent deficiency in Petitioner's case, as both of her experts referenced many items of literature that were never filed for review and consideration as evidence in this action.

[12] *See* Dorland's at 252. Dr. Middleton has represented in both his expert report and trial testimony that Mrs. Olson was diagnosed with bronchiectasis, but the medical records supporting this assertion are fairly thin, as they do not clearly establish when this initial diagnosis was made, nor by whom. However, there are a few references to a bronchiectasis diagnosis being made in the past (Ex. 7 at 1, 26; Ex. 9 at 1). This, coupled with the other documented asthma issues, constitutes sufficient support for concluding as a general matter that Petitioner has chronic respiratory problems. Therefore, whether she actually had bronchiectasis need not be conclusively decided in order to evaluate Petitioner's general contention that her respiratory problems set the stage for a susceptibility to RA.

medical thinking links persistent lung conditions with the initiation of RA. *Id.* at 5-6; *see also* Sofat. In particular, certain protein complexes common to the joints and synovial spaces (forming the extracellular matrix or "ECM") were also expressed in the lung, and have been closely associated with the tissue and cartilage destruction characteristic of RA. *Id.* at 6-7. Lung inflammation has also been associated with the generation of ACPAs – even though, as noted above, Mrs. Olson has repeatedly tested negative for this autoantibody.

Sofat was referenced several times during the entitlement hearing and provides some general guidance about elements of Petitioner's causation theory. *See, e.g.,* Tr. at 41, 43, 72, 76. Sofat is a review article summarizing the findings of other studies linking citrullination in the lung to the autoimmune processes resulting in RA. In particular, Sofat discusses a number of ECM proteins, like fibronectin and fibrinogen, that are found both in the lung and joints, and which either participate in the processes leading to RA or have been found in citrullinated form in RA synovial tissue. Sofat at 2. Sofat's authors proposed that "it is possible that primary citrullination occurs outside the synovium" and could in fact begin in the lung, which is "susceptible to inflammatory responses triggered by infection and autoimmunity." *Id.* at 3. Thus, an individual with preexisting lung and respiratory conditions could later develop RA – if the right impetus to start the process occurred.

Based upon the above, Dr. Middleton proposed several possible mechanisms by which the HPV vaccine might trigger the autoimmune process leading to RA. He noted that individuals with RA often were in possession of some of the antibodies believed implicated in the process (but which he had previously admitted Mrs. Olson lacked)[13] for years before they displayed outward clinical symptoms. Second Middleton Rep. at 9-10. Introduction of a variety of environmental factors – including vaccination – could then trigger the autoimmune and inflammatory processes. *Id.* at 10-11, *citing* V. Molina and Y. Shoenfeld, *Infection, Vaccines and Other Environmental Triggers of Autoimmunity,* 38 Autoimmunity 235-45 (2005) (filed as Article 4) ("Molina").

Here, Dr. Middleton maintained that a single specific component of the HPV vaccine was the trigger: alum, an adjuvant included in the HPV vaccine due to its ability to elicit an immune response. *Id.* at 11-12.[14] In support, he referenced several pieces of literature exploring the precise

[13] Dr. Middleton did propose that a bacterial infection in one of Mrs. Olson's thumb joints treated by surgical intervention in 2004 – six years before the vaccination at issue – might have produced some unidentified antibodies that, via the biologic mechanism of "bystander activation," could have themselves contributed to the overall autoimmune process alleged to have occurred in this case. Second Middleton Rep. at 7-9. He did not, however, revisit this point in his hearing testimony – and taking into account Dr. Middleton's lack of particularized expertise on the topic of immunology, I find it speculative, and therefore not appreciably helpful in establishing Petitioner's claim.

[14] Dr. Middleton's second report also proposed broadly that protein components of the HPV vaccine might, via the process of molecular mimicry, have had sufficient homology with self-proteins to encourage the production of autoantibodies involved in the pathogenesis of RA. Second Middleton Rep. at 13-14. The literature cited for this proposition, however, mostly involved individuals possessing the ACPAs that Mrs. Olson indisputably lacks. *Id.* at 14 n.31. Moreover, Dr. Middleton expressly acknowledged under cross-examination that the causation theory he was

means by which alum accomplishes its immune system-stimulating function. Middleton Rep. at 12; *see also* R. Goldbach-Mansky, *Immunology in Clinic Review Series; Focus on Autoinflammatory Diseases: Update on Monogeneic Autoinflammatory Diseases: the Role of Interleukin (IL)-1 and an Emerging Role for Cytokines Beyond IL-1,* 167 Clinical and Experimental Immunology 391-404 (2011) (filed as Article 5) ("Goldbach-Mansky"); H. Li, *Cutting Edge: Inflammasome Activation by Alum and Alum's Adjuvant Effect are Mediated by NLRP3,* 181 J. Immunol. 1-12 (2008) (filed as Article 6) ("Li"); L. Franchi and G. Nunez, *The NLRP3 Inflammasome is Critical for Alum-Mediated IL-1β Secretion but Dispensable for Adjuvant Activity,* 38 Eur. J. Immunol. 1-7 (2008) (filed as Article 7) ("Franchi").

Underlying the contention that alum could trigger autoimmunity was scientific literature exploring the innate immune response (as opposed to the adaptive response, whereby the human immunologic system learns to manufacture antibodies to foreign pathogens that a given vaccine presents in a non-pathologic form based upon the vaccine's protein-based components) and alum's role in provoking it. Dr. Middleton proposed that certain protein complexes – NLRP3 inflammasomes – were key to igniting the autoimmune process relevant to RA's pathogenesis. Petitioner's filed literature defines an inflammasome to be "a high molecular weight complex that activates inflammatory caspsases and the cytokine IL-1β." F. Martinon et al., *The Inflammasomes: Guardians of the Body*, 27 Annu. Rev. Immunol., 229-65 (2009) (filed as Article 10) ("Martinon") at 237. Once such inflammasomes were activated by alum contained in a vaccine, an inflammatory process that Dr. Middleton alleged was central to RA began, because the inflammasomes themselves mediated the release of other proinflammatory cytokines that fueled the process. Middleton Rep. at 12-13. He thus posited that because alum has been demonstrated to stimulate these kinds of inflammasomes known to be factors in RA, there is a causal relationship between the vaccine and the pathogenesis of RA.

The literature specifically referenced to support the contention that alum was a plausible triggering factor in the cause of RA actually said far less on the topic than Dr. Middleton or Petitioner assumed, however. Goldbach-Mansky primarily focused on monogenic autoinflammatory diseases – a group of rare hereditary disorders distinguishable from RA. Monogenic autoinflammatory disorders are characterized by clinical and biological inflammatory syndromes in which there is little or no evidence of autoimmunity (for example, the presence of autoantibodies as measured by testing). Goldbach-Mansky at 392. Such conditions (which have an identified genetic underlying cause) are greatly influenced by stimuli (including an alum adjuvant) capable of activating the NLRP3 inflammasome, and an individual suffering from that condition lacks the capacity to neutralize or balance the process initiated by the stimulated

propounding did not rely on identification of any components of the HPV vaccine other than the alum adjuvant as implicated in causing RA. Tr. at 64 ("I don't think there is good scientific information that [other components of the HPV vaccine] are related"). I accordingly deem this element of his second report to have been abandoned, speculative, and/or too far outside of Dr. Middleton's primary expertise to constitute a reliable proposition for Petitioner's causation theory.

inflammasome (due to the same "intrinsic activating mutations" that cause the condition in the first place). *Id.* at 392, 394. But this is not comparable to RA, which not only has identifiable autoimmune biomarkers but also is not similarly monogenic (even if genetic risk factors can play some role in the condition's development). Indeed, treatments proposed in Goldbach-Mansky as effective in blocking cytokines promoted by the inflammasome (*Id.* at 400) have not yet been shown to be applicable to a disparate condition like RA. And Goldbach-Mansky does not address RA or state that its findings bear on that condition.

Other literature that Petitioner and Dr. Middleton offered on this point focused more on the general role that alum plays as an adjuvant than its supposed pathogenic potentiality. Li, for example, begins by characterizing alum's "adjuvanticity" as "poorly understood," but goes on to explore via an animal study how it might actually work. Li at 1-2. Although Li concludes that alum's activation of certain cytokines is mediated by the NLRP3 inflammasome, it says nothing about whether this process could be pathogenic with respect to *any* disease, let alone RA. Franchi, via another animal study, similarly observed that alum triggered activation of the NLRP3 inflammasome, but also noted that the adjuvant's role in promoting the production of certain antibodies could be accomplished without the inflammasome's involvement. Franchi at 1-2. Franchi thus did not address whether alum could stimulate production of proinflammatory cytokines in a sustained enough manner to be pathogenic.

Finally, Dr. Middleton's second report addressed the timing of onset of Petitioner's symptoms in light of the timeframe in which RA would be expected to occur under her theory of causation. Second Middleton Rep. at 17-18. He contrasted the fact that Petitioner had no symptoms before she received the HPV vaccine in July 2010, but then (based on her own statements as well as statements contained in medical records beginning five to six months after) began to experience pain and swelling a week or two after vaccination. *Id.* at 18. Dr. Middleton proposed that this timeframe was medically acceptable, analogizing the onset of Petitioner's RA to macrophagic myofasciitis ("MMF"), an immune-mediated condition in which the alum adjuvant has also been implicated and in which onset has been proposed to be possible as long as years after vaccination. *Id.*, *citing* E. Israeli et al., *Macrophagic Myofasciitis: A Vaccine (alum) Autoimmune-Related Disease,* 41 Clinic. Rev. Allerg. Immunol. 163-68 (2011) (filed as Article 8) ("Israeli"). Israeli, however (similar to Goldbach-Mansky), involved a different disease, characterized by a "local-stereotyped and immunologically active lesion in the site of inoculation (deltoid muscle)," and also found specific evidence of the alum remaining at the vaccine administration site based on muscle biopsy. Israeli at 163, 166-67.

Dr. Middleton's third and final report was filed in January 2017. It mainly offers some additional explanation bulwarked by new literature in support of the component of his theory pertaining to the NLRP3 inflammasome and its posited role in RA's development. Third Middleton Rep. at 1-2. He alleges that the inflammasome is "centrally involved in allergic lung

inflammation" of the kind Petitioner suffers from, via its activation of proinflammatory cytokines as well as other T-cells, and thus the putative activation of the inflammasome by the alum contained in the HPV vaccine would trigger this process. *Id.* at 2, *citing* A.-G. Besnard et al., *NLRP3 Inflammasome is Required in Murine Asthma in the Absence of Aluminum Adjuvant,* 66 Allergy 1047-57 (2011) (filed as Article 14) ("Besnard"). Lung inflammation would also in theory encourage production of ECM proteins that are involved in the destruction of cartilage and joint tissue central to RA. Third Middleton Rep. at 2. But, as with other literature offered in this case, Besnard does less for Petitioner's theory than Dr. Middleton proposes. Besnard is an animal study that confirmed the importance of the NLRP3 inflammasome in the pathogenesis of asthma by *excluding* alum from its experiment "to avoid any overlapping effect of this strong NLRP3 activator," so that the study could identify the inflammasome's specific role. Besnard at 1053, 1055. Besnard does not stand for the proposition that alum is itself a sufficient trigger of the inflammasome to be pathogenic.

At hearing, Dr. Middleton largely summarized the contents of his reports, confirming his history of treating Mrs. Olson since 2013 until the present and reiterating his views as to the role the HPV vaccine played in her RA. *See generally* Tr. at 30-109. He referenced one point more forcefully addressed later by Dr. Mayer, but only briefly touched upon in his written reports (*see, e.g.*, First Middleton Rep. at 6-7): that existing epidemiologic evidence suggesting no relationship between the HPV vaccine and RA is unreliable.[15] Dr. Middleton stressed the fact that even though he was aware of such studies, Petitioner did not fit into the younger age cohort of individuals studied, reducing the applicability of findings from such studies to this case. Tr. at 79.

Dr. Middleton's testimony also acknowledged many of the limitations of Petitioner's theory. He claimed that there existed studies focused on the causal role of alum in the pathogenesis of RA, but admitted he was unaware of any that had been filed in the case. Tr. at 62-63. And he accepted that some of the literature that Petitioner offered mainly spoke to the intended role that alum played as an adjuvant in stimulating the innate immune system in a biologically proper manner, rather than to its alleged capacity to instigate a pathogenic process (*see, e.g.,* Tr. at 69 ("[s]o the reason that [the inflammasome]'s there is to provide a response. It helps to make the vaccine more effective") – although he maintained that individuals susceptible to RA would potentially experience an "exaggerated response" to the adjuvant regardless. Tr. at 69. He further agreed that it was speculative to propose that Petitioner had some underlying genetic predisposition to developing RA. Tr. at 64.

Dr. Middleton was pressed on the extent to which aspects of Petitioner's theory even applied to Petitioner. Thus, he acknowledged that his "trigger" theory about the impact of the alum

[15] Because Dr. Mayer was far more qualified to opine on such matters, and because (as discussed below) Respondent has not offered epidemiologic evidence possibly rebutting some of Petitioner's contentions in this case, I do not address in detail Dr. Middleton's arguments herein regarding alleged deficiencies of such studies.

adjuvant was more relevant to "people who develop antibodies to citrullinated proteins" – a group not including Petitioner. Tr. at 75-76. He nevertheless maintained that Mrs. Olson was susceptible to RA, although he could not predict that, absent the HPV vaccine, she would have developed the disease in any event. Tr. at 81 ("[i]t's possible that something else in the future may have triggered it, but it's also more likely that nothing ever would have.")

Finally, Dr. Middleton admitted that he largely relied on the temporal relationship between receipt of the HPV vaccine and Petitioner's subsequent development of RA to corroborate his theory. Tr. at 78. When specifically asked to identify evidence from the medical record establishing that "the theory you've proposed actually happened [to] Ms. Olson," he responded that "I think what you're asking me is something that's impossible in anyone," maintaining that it was contrary to "the way medical science works" to ask him "to prove in an individual patient that these things happened." Tr. at 80.

3. *Dr. Lawrence Mayer* – Petitioner also offered a single written report from Dr. Mayer that was intended to address certain epidemiologic evidence relevant to her causation theory (although – importantly – never offered in this case, or relied upon by Respondent). *See* Mayer Report, dated September 25, 2015 (ECF No. 39) ("Mayer Rep.").

As Dr. Mayer's report indicates, he has been a medical doctor since 1970; he obtained his B.S. in psychology and pre-med, M.S. in mathematics, and Ph.D. in mathematics, statistics, and biostatistics from The Ohio State University. Mayer Rep. at 1. He finished and obtained his M.D. in England and subsequently worked for the British Health Service studying psychiatry and epidemiology. Tr. at 117. He is currently employed as a professor at Johns Hopkins University Bloomberg School of Public Health and School of Medicine, a professor of epidemiology at the College of Public Health, University of Arizona, and a professor of biostatistics, economics, and biomedical informatics at Arizona State University. *Id.* Dr. Mayer has a focused expertise in epidemiology, and he was in fact retained to offer such an opinion in this case. Mayer Rep. at 2. Thus, although Dr. Mayer reviewed Mrs. Olson's medical records in formulating his opinion, such review largely did not inform the core of his opinion (with one exception addressed below).

Dr. Mayer opined that in fact the HPV vaccine did cause Mrs. Olson's RA, but his conclusion was indirectly derived, rather than the product (as with Dr. Middleton's opinion) of a causation theory explaining how the vaccine might result in the disease. As he observed, not only had Mrs. Olson received the vaccine for an "off-label" purpose (the treatment of warts), but also the vaccine itself was indicated for *prevention* of certain diseases, not treatment of them – facts that he deemed meaningful in assessing the vaccine's capacity to injure. Mayer Rep. at 3-5.

Dr. Mayer was, however, more specific about the putative risks of the vaccine in addressing Petitioner's circumstances. He began by noting that "Gardasil has not been shown to be safe and

effective for women over 26 who are exposed to HPV," and in fact is indicated mainly for young and adolescent women who have not yet been exposed to the virus. Mayer Rep. at 5. Thus, the vaccine has yet to be tested for women outside the targeted age group, like Petitioner. *Id.* at 7-9. From this, Dr. Mayer concluded that the vaccine was in fact *not* safe for Petitioner, based on "scientific and statistical principles." *Id.* at 9. In addition, the vaccine's safety is uncertain for "immunocompromised individuals" – a category Dr. Mayer assumed included Mrs. Olson due to her use of steroidal medications to treat her chronic lung/respiratory problems, since "[s]teroids work by suppressing the immune system." *Id.* at 8.

Dr. Mayer next discussed several epidemiologic studies relevant to HPV's safety. First, he offered a study from Denmark and Sweden that he purported demonstrated (in a population of girls 10-17 years old) a higher incidence of RA among those vaccinated than not, although he acknowledged that the differential between the relevant incidence rates was not statistically significant enough to constitute strong evidence about the vaccine's risks. Mayer Rep. at 10, *citing* L. Arnheim-Dahlstrom et al., *Autoimmune, Neurological, and Venous Thromboembolic Adverse Events after Immunisation of Adolescent Girls with Quadrivalent Human Papillomavirus Vaccine in Denmark and Sweden: Cohort Study*, 347 BMJ 5906 (2013).[16] Dr. Mayer also referenced passive reporting system evidence alleging adverse events after receipt of the HPV vaccine (much like the VAERS data Dr. Middleton's reports evaluated), although he acknowledged that from an epidemiologic standpoint, such evidence was of relatively low probative value. Mayer Rep. at 14.

Dr. Mayer's report discusses at length what he termed the "Merck study" – C. Chao et al., *Surveillance of Autoimmune Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine,* 271 J. Intern. Med. 193-203 (2012) (filed as Article 29) ("Chao"). Chao (funded but not authored by Gardasil's manufacturer, Merck & Co.) was a peer-reviewed observational study[17] analyzing a database comprised of the medical histories of approximately 189,000 women (members of two of Kaiser Permanente's managed care health organizations in the State of California) to determine whether the studied population had developed a variety of autoimmune conditions[18] after receiving the Gardasil vaccine. Chao at 194. The researchers

[16] Dr. Mayer's expert report was not accompanied by the filing of *any* of the items of literature referenced therein, and Petitioner later filed only one of the epidemiologic studies he referenced – making it very difficult for me to assess if he has properly attributed their findings. Because, however, I ultimately did not find Dr. Mayer's opinion to be useful in resolving this case, the absence of support for the opinions he proposes is a moot point.

[17] In an observational epidemiologic study, researchers analyze groups of individuals who were exposed to a test agent, comparing them with groups not so exposed. Michael D. Green et al., "Reference Guide on Epidemiology," in *Reference Manual on Scientific Evidence* 549, 555-56 (3d ed. 2011). Chao's investigators drew inferences about the side effects of Gardasil based on historic data, where the assignment of subjects into a treatment group (women who received the Gardasil vaccine) versus a control group (women who did not) was outside of the investigators' control. *See* Chao at 194.

[18] The diseases monitored in Chao included rheumatologic/autoimmune disorders, including immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, RA, and JRA. Chao at 194.

compared the results of the studied vaccinated population with unvaccinated, similarly-situated individuals also enrolled with Kaiser Permanente in Southern California, in order to compare incident rate ratios for the identified autoimmune conditions. *Id.* at 194-95. Chao did not observe an increased risk of developing RA (or other autoimmune conditions) following receipt of the Gardasil vaccine (*Id.* at 196, 201), but Dr. Mayer nevertheless opined that the studied population was not comparable to Petitioner's circumstances, for reasons similar to what Dr. Middleton had argued. Mayer Rep. at 12-13.[19]

Dr. Mayer testified at the entitlement hearing, albeit only briefly. He reiterated his overall point that he discounted the existing epidemiologic evidence suggesting no link between RA and the HPV vaccine for the reasons mentioned, and that he therefore questioned the use of such evidence to vouch for the vaccine's safety. Tr. at 122-23. He emphasized again that in Mrs. Olson's case, the vaccine had been used for a non-indicated purpose (*Id.* at 125), and that the epidemiologic studies that existed, such as Chao, simply were not applicable since the determinations they proposed were based on population samples that excluded people like Petitioner. *Id.* at 126, 129-30.

B. Respondent's Witness: Dr. Robert Lightfoot

Dr. Lightfoot acted as Respondent's sole witness and expert in this action, filing two reports as well as testifying at the entitlement hearing. *See* Report, dated May 15, 2015 (ECF No. 35-1), filed as Exhibit A ("Lightfoot Rep."); Second Report, dated March 31, 2016 (ECF No. 48-1), filed as Exhibit E ("Second Lightfoot Rep."). As his CV indicates, Dr. Lightfoot graduated from Vanderbilt University with a Bachelor of Arts degree in 1958, and then attended Vanderbilt's School of Medicine, graduating in 1961. ECF No. 35-2 (filed as Exhibit B) ("Lightfoot CV") at 1. Dr. Lightfoot then interned at the Columbia Presbyterian Medical Center from July 1, 1961 to June 30, 1962, completing a residency there before returning to Vanderbilt in 1964 for a subsequent residency. *Id*. He then held a fellowship in rheumatology (his present specialty) at Columbia University from July 1, 1964, to June 30, 1966. *Id.* He subsequently served as Chief of the Rheumatology Division at the Medical College of Wisconsin from 1976 to 1986, where he also taught. *Id*. at 2. Dr. Lightfoot thereafter served as Division Director of the Allergy, Immunology, and Rheumatology Division at the University of Kentucky at Lexington, and as a professor of Medicine and a professor of Medicine Emeritus at the University of Kentucky, College of Medicine. *Id.*

[19] Dr. Mayer's report raised other questions about the reliability of Chao based on its methodology, but because I accept Petitioner's point about its reduced probative value in this case (and given that Respondent has not offered it to rebut Petitioner's claim), I need not address such additional challenges to the weight this evidence should be given. In prior cases, however, I have found that Chao is reliable science relevant to claims that the HPV vaccine injured a young woman who *would* be included in the age group the study considered. *See, e.g., Sullivan v. Sec'y of Health & Human Servs.*, No. 10-398V, 2015 WL 1404957, at *19-20 (Fed. Cl. Spec. Mstr. Feb. 13, 2015).

Dr. Lightfoot is board certified by the American Board of Internal Medicine and the American Board of Internal Medicine in rheumatology, and he is a licensed physician in Kentucky. Lightfoot CV at 1. He is a member of the American College of Rheumatology and has co-authored 41 peer-reviewed articles, which are listed on his CV. *Id.* at 3, 14–18. Dr. Lightfoot has extensive experience treating individuals with RA (Tr. at 140), but he is not an immunologist. Tr. at 227.

Dr. Lightfoot's primary written report is based on a review of the medical records plus Dr. Middleton's first report. As confirmed at hearing, he opines that Petitioner's RA was idiopathic in origin, and he disputes that the evidence shows any relationship to her receipt of the HPV vaccine. Tr. at 224-25. Dr. Lightfoot generally termed Petitioner's RA as relatively mild, based on his examination of her medical records (which he felt did not display a severe case of the condition, given the low inflammation levels her testing revealed) as well as her demonstrated ability to remain active despite the pain. Lightfoot Rep. at 5. Petitioner's underlying respiratory problems, and the steroidal treatments she received for them, might in fact have (in his view) blunted her overall symptoms as well as her specific initial onset. *Id.*

Much of Dr. Lightfoot's primary written report was aimed at rebutting Dr. Middleton's proposed causation theory. Thus, he attacked the concept that Mrs. Olson's early onset after vaccination was proof of a causal link to the HPV vaccine as *post hoc ergo propter hoc* reasoning, and he questioned overall whether Petitioner's theory was supported by reliable evidence (for example, in the form of an identified antigen in the vaccine that might have initiated an autoimmune reaction). Lightfoot Rep. at 5-6. He attacked the statistical significance of vaccine risks identified on the vaccine package insert and also questioned whether VAERS data was useful in establishing causation. *Id.* at 6. And he attempted to defend the statistical evidence like Chao – although neither Drs. Lightfoot nor Middleton, as RA specialists, were particularly qualified to opine on the reliability of a large scale epidemiologic study. *Id.* at 7.

Dr. Lightfoot's second report was a point-by-point review of certain aspects of Dr. Middleton's second report. *See generally* Second Lightfoot Rep. Dr. Lightfoot began with an overall explanation of RA, noting that it is a very common disorder in which no etiologic cause has been defined. Second Lightfoot Rep. at 2. Dr. Lightfoot then addressed Dr. Middleton's several references to Petitioner's supposed genetic predisposition to RA. *Id.* While Dr. Lightfoot acknowledged that genetic factors in families can create a predisposition to RA, he noted that fact is irrelevant to this case. *Id.* at 2-3. There is no evidence that Petitioner's relatives had ever been tested or found positive for genetic factors, and Petitioner herself did not possess RA-associated antibodies. *Id.* at 3. Due to the lack of any evidence in the medical records revealing a family history of arthritis, he disputed the accuracy of such assumptions. *Id.*

Dr. Lightfoot next addressed Dr. Middleton's supposition that Petitioner's medical records revealed no other possible environmental trigger than the HPV vaccination, and thus it must have

been the cause. Second Lightfoot Rep. at 3. However, Dr. Lightfoot maintained that *no* RA patients have a proven causative environmental trigger, and while it might be convenient to select the "nearest suspect in time," it is not possible to know the exact trigger. *Id.* He also reiterated that a causal relationship cannot be proven simply because Petitioner's onset of arthritis symptoms was close in time to the vaccination. *Id.* at 4. Dr. Lightfoot went on to also explain that while he agreed with Dr. Middleton that there is a connection between pulmonary inflammation and RA, it occurs in unvaccinated individuals as well, and that respiratory problems do not necessarily predispose an individual to developing RA. *Id.* He also disagreed with Dr. Middleton's focus on the antibodies to citrullinated proteins in RA individuals, asserting that there was no evidence that elevated levels of the CCPA autoantibodies are specific to a certain virus or other infectious agent. *Id.* at 5. Finally, Dr. Lightfoot suggested that, in fact, Petitioner's clinical presentation better fit the features of spondyloarthopathy syndrome. *Id.* at 5-6. This syndrome's treatment is similar to RA, and the causation discussion would be the same as RA, as it follows no recognizable antecedent event. *Id.*

At trial, Dr. Lightfoot's brief oral testimony on direct examination tracked his report, re-emphasizing that the cause of Petitioner's RA was unknown. Tr. at 148. He seemed to allow for the possibility that her preexisting lung and respiratory problems could be connected to her subsequent RA, but he questioned whether generalized lung inflammation had been adequately linked to joint damage to relate them causally. *Id.* at 147. In response, Petitioner's counsel devoted the majority of cross-examination to attempting to obtain Dr. Lightfoot's concession as to the reasonableness of numerous statements and factual or scientific points set forth in a variety of Petitioner's items of literature relating to the immunologic aspects of her theory. *See, e.g.,* Tr. at 150-69.

Petitioner largely succeeded in this task. Dr. Lightfoot was hard-pressed to deny the reasonableness or accuracy of many of the statements contained in Petitioner's literature when put before him. *See, e.g.,* Tr. at 168-69 (Dr. Lightfoot, shown a portion of Besnard, confirmed that he had no basis upon which to disagree with the statement that "the alum adjuvant is a strong NLRP3 activator"). Yet this approach to impeaching Dr. Lightfoot was of limited effectiveness – for the same expertise limitations that reduced the evidentiary value of Dr. Lightfoot's statements about the causal role of the HPV vaccine herein *also* limited the weight that can be given to his admissions about the contents of articles dealing with immunology. And in any event (and as discussed in greater detail below), the fact that components of Petitioner's theory were facially sound or reliable (and that Respondent's expert on the injury at issue conceded certain points relevant to the science behind Petitioner's causation theory) does not lead to the conclusion that the theory *as a whole* is reliable or persuasive.

IV. Procedural Background

After initiating this action in July 2013, Mrs. Olson began filing medical records in support of her claim, completing the process approximately one year later. Respondent's Rule 4(c) Report was then filed on September 15, 2014 (ECF No. 30). Petitioner was ordered to file an expert report by December 31, 2014, and she did so with the filing of Dr. Middleton's Declaration in January 2015. ECF Nos. 32 and 33. I thereafter ordered Respondent to file an expert report, which he did on May 15, 2015. ECF No. 35.

I subsequently instructed Petitioner to file a supplemental expert report aiming to bulwark her causation theory as well as to better explain how onset of her RA related to the course of the condition. *See* Order, dated May 21, 2015 (ECF No. 36). After some extensions of time were requested and granted, Petitioner filed Dr. Mayer's report on September 28, 2015 (ECF No. 39). But, after review of the new report, I held another status conference in which I reiterated my previously-expressed concerns about gaps in Petitioner's theory and invited her to supplement her expert report again. *See* Order, dated October 5, 2015 (ECF No. 40). Petitioner then filed a second expert report from Dr. Middleton on December 1, 2015 (ECF No. 41).

In 2016, Respondent opted to file a second report from Dr. Lightfoot on April 1, 2016 (ECF No. 48). By this point, the parties also had discussed potential hearing dates, and an entitlement hearing was set for March 27-28, 2017. Order, dated March 31, 2016 (ECF No. 47). Petitioner also filed a third expert report from Dr. Middleton on January 14, 2017. ECF No. 49-1. The hearing went forward as scheduled, and the parties agreed that no post-hearing briefing was necessary. This matter is now ripe for a decision.

V. Applicable Law

A. Petitioner's Overall Burden in Vaccine Program Cases

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[20] In this case, Petitioner does not assert a Table claim.

[20] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005): "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d

1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).[21]

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant

[21] Although decisions like *Contreras* suggest that the burden of proof required to satisfy the first *Althen* prong is less stringent than the other two, there is ample contrary authority for the more straightforward proposition that when considering the first prong, the same preponderance standard used overall is also applied when evaluating if a reliable and plausible causal theory has been established. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1350 (Fed. Cir. 2010).

proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Evidence

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993

F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms.").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs*., 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y of Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial for a (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 91997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special

masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. Consideration of Medical Literature

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all of the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case – just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to – and likely undermines – the conclusion that it was not considered").

At the same time, and as previously noted, there were many items of literature that Petitioner's experts referenced in the action that were not filed as part of the record in this case. *See, e.g.,* Tr. at 62-63. While in a few such instances, I have considered an unfiled or late-filed item[22] because of its apparent significance to Petitioner's claim, I have not attempted to locate and then review every single unfiled item cited in this case —and am not otherwise obligated to do so, consistent with the fact that Program claimants are not required to produce medical literature to establish causation. *See Capizzano*, 440 F.3d at 1324; *Althen*, 418 F.3d at 1280. Petitioners are responsible for raising with the special master those items that they deem important enough to constitute favorable relevant evidence, and ensuring that they are included in the evidentiary record, if they want them considered. *See, e.g., Cedillo*, 617 F.3d at 1347 (special master did not err in disregarding articles where no experts gave any testimony as to the "validity or import" of such article).

ANALYSIS

[22] To give the most notable example, from the time of the filing of Dr. Middleton's first expert report in December 2014, Petitioner and her experts repeatedly referenced Chao, in an effort to undermine its probative weight as an epidemiologic study casting doubt on any relationship between the HPV vaccine and autoimmune conditions such as RA – and yet she did not file it until *after* the hearing this year. *See* ECF No. 62 (Medical Articles Appendix, filed March 31, 2017).

Although Petitioner credibly established that onset of her RA most likely began within one or two weeks of her receipt of the HPV vaccine, this finding alone is not a sufficient basis upon which to prevail. Rather, she needed to show that (a) the HPV vaccine *could* cause RA, and (b) that it did so in her case. She was unable to meet either of these *Althen* test prongs.

A. *Althen* Prong One

My discussion of Petitioner's causation theory begins with what she acknowledges is missing from that theory. She explicitly does not claim that any protein component specific to the HPV vaccine is implicated in her theory. *See, e.g.,* Tr. at 52-53, 64. Petitioner has also offered no evidence that the HPV vaccine has ever been associated with RA (although, as discussed below, she has offered expert testimony intended to rebut the *opposite* conclusion). Of course, Program petitioners are not required to offer direct proof supporting their theory, or even any specific type of evidence, but instead may rely on circumstantial evidence. *See, e.g., Althen,* 418 F.3d at 1280. Regardless of *what* kind of evidence is relied upon, however, claimants must still establish preponderant proof. And in addressing the first *Althen* prong, that proof must go toward establishing a reliable scientific or medical theory – and if it comes in the form of a scientific or medical article, it must be reliable. *Knudsen*, 35 F.3d at 548.

There are several interlocking components of Petitioner's theory. First, she maintains that certain individuals with preexisting conditions – here, persistent lung infections or asthma – are more likely to develop RA. The lung, she maintains, can be the situs of the development of a process (as evidenced by the presence of ACPAs or some other, not-yet-identified antibodies) that greatly contributes to the chronic, autoimmune inflammatory state that allows the cellular destruction directly responsible for the pain and visible clinical symptoms associated with RA. The fact that there are similarities between the ECMs in the lung and those found in synovial locations further supports the contention that a pathologic process beginning in the lungs could impact the joints under Petitioner's theory.

Second, Petitioner asserts that vaccines can function as the trigger that sets off the autoimmune process resulting in RA – particularly due to the inclusion of alum as an adjuvant. Scientific research associates alum with the increased production of certain cytokines that are involved in the inflammatory process leading to RA. Key to this process are the proinflammatory cytokines like IL-1 that Petitioner posits play an integral role in allowing the chronic inflammatory conditions in which a person susceptible to RA will then experience it. The production of those cytokines is mediated by the NLRP3 inflammasome – which is stimulated by alum. Thus, she theorizes, the HPV vaccine's capacity to stimulate the innate immune system in an individual like herself is the causative factor that would produce RA.

A few overarching aspects of this theory are medically or scientifically sound. Petitioner has offered persuasive evidence in support of her contention that persistent lung inflammation is often associated with RA. In addition, her explanation for the role ACPAs play (as primarily set forth in the filed literature) in causing RA, and the likelihood that the citrullination that precedes ACPA production occurs in the lung, is logical and scientifically reliable. She also offers trustworthy articles exploring the not-fully-understood processes by which adjuvants like alum help stimulate the innate immune system, thereby increasing the efficacy of vaccines. She has established that cytokines play *some* role in the process of encouraging the unchecked inflammation that is so integral to RA's development. And inflammasomes have been shown herein to play a mediating role in the overall immune reaction process. Martinon at 242.

Where Petitioner's theory falters, however, is in its specifics, for many of its most important elements are inadequately supported. First, Petitioner has failed to demonstrate that cytokine upregulation allegedly resulting from vaccine administration is *itself* a trigger for RA, rather than either a byproduct or subsequent component of the disease. Instead, Petitioner has established a general point – that many different environmental factors could initiate the process that would cause a susceptible individual to develop RA, and that it is not unreasonable to consider a vaccine (like a wild virus infection) as one of those factors. But it remains a speculative issue as to whether cytokine production instigated by a single vaccine containing alum would be robust enough, and occur for long enough, to be pathogenic generally, let alone to cause RA.

Reliable scientific support is also lacking for Petitioner's argument that the alum included as an adjuvant in a wide variety of vaccines is the pathogenic key herein. As noted above, and by the admission of Petitioner's experts, this is the *sole* HPV component implicated in their causation theory (or at least the only one they were able to identify as possibly causative). It was therefore critically important that Petitioner marshal reliable scientific or medical evidence suggesting that alum could precipitate RA or some other comparable autoimmune disease. But the literature Petitioner offered – the most scientifically-reliable items of which were studies aimed at understanding *how* alum performs as a stimulatory actor in the immune process – does not do this. *See, e.g.,* Li; Franchi; Martinon. Rather, such studies explore in detail a known fact: that alum is an effective adjuvant in its stimulation of the immune system, and hence such research helps science understand why it is included in vaccines in the first place. They do not permit the broader conclusion that Petitioner urges: that alum can be pathogenic – and indeed *none* of Petitioner's offered literature so proposes.[23]

[23] Israeli – the article about MFF – is the closest Petitioner and her experts come to establishing some possible pathogenic role for alum. But that article involves an entirely different disease, and one in which the muscle biopsies have established that alum remained at the injection site – a showing that has not been made here, or (at least based on Petitioner's literature) in <u>any</u> RA cases. Israeli's findings are thus too narrowly focused upon a different disease to be applicable.

The articles referencing the general capacity of alum to stimulate inflammasomes, or the possibly pathogenic role of over-stimulation of inflammasomes, do not fill this gap. They do not establish that such stimulation by alum alone, in levels found in a vaccine, is pathogenic in connection with a disease like RA (as opposed to distinguishable diseases such as those discussed in Goldbach-Mansky). Literature that shows that inflammasomes are important to the tissue/ECM destruction or general inflammation that characterize RA does not explain why alum in a vaccine would likely initiate or increase that process. At best, there is some support for the concept that different environmental factors might trigger RA. But there is nothing specific enough regarding *any* of the possible triggers (which include things that the population is broadly subjected to, like UV rays in sunlight) to define how the triggering process would theoretically work, and/or whether all triggers would impact the process in the same way. The fact that many vaccines also contain alum but have not been implicated in RA or other autoimmune conditions as alleged herein also merits some weight. *See, e.g., Johnson v. Sec'y of Health & Human Servs.*, No. 10-578V, 2016 WL 4917548, at *8-9 (Fed. Cl. Spec. Mstr. Aug. 18, 2016) (noting the unreliability of the theory that if an adjuvant can cause an autoimmune disease, it could cause any autoimmune disease). If alum can cause RA, there should be more robust evidence that it is associated with other autoimmune conditions in different vaccines.

An additional problem with Petitioner's theory is the degree to which it relies on science that is ultimately inapposite to the present context. For example, many articles Petitioner offered discuss or address the ACPAs that are the result of citrullination, a process widely understood to be an explanation for RA in numerous cases (and which allows a link to be drawn between chronic lung infections akin to what Mrs. Olson experienced and her RA). But Petitioner has never tested positive for those autoantibodies, and therefore she cannot credibly propose a theory involving a process that she cannot also establish occurred to her. *See* Ex. 2 at 65, 101-02, 104, 106-09, 111. This also impacts Petitioner's argument that an individual with chronic lung infections, due to asthma or other respiratory ailments, is susceptible to a vaccine trigger, since the literature discussing the lung as an initiatory situs for RA largely depends on citrullination occurring there first. *See, e.g.,* Sofat at 3; Ytterberg at 13 ("[t]he data give further support to the hypothesis that immunity to citrullinated proteins may be initiated in the lungs and potentially contribute to inflammation in the joints.").

Similarly, at hearing Petitioner made a point of stressing Goldbach-Mansky (and related articles involving discussions of proinflammatory cytokines) as particularly trustworthy support for her theory, given the authors' employment at the National Institutes of Health (Tr. at 53, 161 ("[s]o you're aware that [Goldbach-Mansky]'s actually an employee of a division of the Respondent")). Yet, as noted above, Goldbach-Mansky involved monogeneic autoinflammatory diseases that far more closely fit the "powder keg" scenario envisioned by Petitioner than does RA, because only in those rare instances has it been more definitely established that an environmental factor like alum might actually initiate a pathogenic process. Certainly Petitioner

offered nothing reliable or persuasive – whether in the form of Dr. Middleton's testimony or from the literature filed herein – that suggests that alum plays any role in abetting the citrullination process (a process that Petitioner and her experts acknowledged might begin years before introduction of a vaccine). *See, e.g.,* Tr. at 41, 48, 75-76.

Petitioner's experts could not ameliorate these deficiencies via their reports or live testimony. Dr. Middleton, though qualified to testify about RA generally and its possible etiology, lacked the specialized immunologic grounding necessary to explain and defend in a persuasive manner the theory articulated in this case, given that theory's dependency on complex immune system processes. The fact that he was a treater, or that his medical training allowed him to comprehend sections of Petitioner's selected items of literature, did not counterbalance his lack of specific expertise relevant to the theory at issue. Program case law makes clear that a treater's opinion is not sacrosanct, but rather subject to the same reliability and weighing considerations that underlie application of the *Daubert* standards to any medical or scientific testimony. *Snyder*, 88 Fed. Cl. at 746 n. 67. I also take note of the fact that Dr. Middleton did not even *begin* to see Mrs. Olson until three years from date of her July 2010 vaccination. *See, e.g.,* Tr. at 31; Ex. 5 at 1. His opinions are thus not the product of real-time observations of her immediate post-vaccination condition – further reducing the deference to be afforded his treater status. *Nuttall v. Sec'y of Health & Human Servs.,* 122 Fed. Cl. 821, 832 (2015) ("[t]he reasoning underlying the finding that opinions of treating physicians should be given particular weight does not apply when . . . the treating physician only saw the patient after the injury and based his opinion on the same evidence as relied upon by the retained experts").

Dr. Mayer for his part raised a few reasonable questions about the relevance of some epidemiologic evidence bearing on the causal relationship between Gardasil and autoimmune conditions like RA. In other cases involving the HPV vaccine, I have found such evidence (particularly Chao) probative and reliable. *Sullivan*, 2015 WL 1404957, at *19-20. Here, however, Petitioner's point about the inapplicability of such studies to an older individual was persuasive. But that was a narrow success, since Respondent does not rely on Chao to defend against Petitioner's claim.

Otherwise, Dr. Mayer's testimony did not appreciably assist Petitioner in establishing a causal relationship between the vaccine and RA, as he lacked the qualifications to reliably opine on such matters. And some of his other arguments (*e.g.*, that the HPV vaccine, since it has *not* been shown to be conclusively safe, might carry risk nonetheless, or that a non-indicated use of a vaccine as occurred here could be dangerous) were not germane to the standard of proof governing a non-Table claim, which focuses only on whether the vaccine caused injury. *See* Section (b)(1)(C)(ii)(I).[24]

[24] Under the Act, evidence of a physician's mistaken administration of the wrong vaccine – the flu vaccine in place of a DTaP vaccine, for example – would not help establish a cause of action if the petitioner could not also establish that

B. *Althen* Prong Two

Pursuant to Petitioner's causation theory, receipt of the HPV vaccine was enough of a trigger, given her underlying circumstances, to initiate a process that ultimately led to a diagnosis of RA. But her medical history does not provide the corroboration necessary to conclude that Petitioner's theory worked out as predicted – and leaves open the possibility that other factors were more likely to have precipitated her RA than the vaccine.

Most significantly, the record does not reflect the existence of an ongoing inflammatory process that would establish the persistent, pathogenic cytokine upregulation that Petitioner's theory envisions after administration of an alum-adjuvanted vaccine. Overall, as Dr. Lightfoot observed in his report, Mrs. Olson's case of RA was on the mild end of the spectrum – reflected in its lengthy course, her ability to tolerate the associated pain while conducting her life, and the lack of evidence demonstrating a more progressively severe trajectory. Petitioner has also pointed to no testing results or other laboratory proof (primarily in the first six months to a year after vaccination) that would establish that her causation theory was occurring as expected, such as results evidencing the presence of ongoing inflammation.[25]

Also missing are other pieces of proof that, under Petitioner's causation theory, should have been reflected in the medical records. In particular, Petitioner has consistently tested negative for ACPAs – even though citrullination, and its connection to persistent inflammatory conditions in the lung, was repeatedly referenced in both Petitioner's literature and Dr. Middleton's testimony as significant in establishing an individual's susceptibility to RA given longstanding respiratory problems. *See, e.g.,* Sofat at 1; Tr. at 45-46. The literature cited about the connection between the lung and RA repeatedly talks of citrullination as occurring specifically in the lung – but here, it cannot be determined that this even occurred in Mrs. Olson's case, absent a finding of the autoantibodies' presence. It is not enough to speculatively propose, as Dr. Middleton did, that there must be some other, "unidentified," antibodies at work in the process. Tr. at 76, 78.[26]

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the mistakenly-administered vaccine injured him, despite the literal "non-indicated" use of a vaccine. In contrast, the administration of the correct vaccine in a mechanically-improper way that causes injury *does* establish a specific kind of claim (a shoulder injury resulting from vaccine administration, or "SIRVA" claim), even if the vaccine otherwise performs as intended from an immunologic standpoint.

[25] Of course, the absence of testing that would not otherwise have been considered so early on given Petitioner's initial, somewhat mild symptoms is not something that deserves excess weight, but it also does not demonstrate the existence of an active immune-mediated disease course.

[26] Petitioner attempted to argue at hearing, through Dr. Middleton, that not all antibodies possibly associated with RA may have been identified to date, thereby minimizing the significance of the absence of ACPAs herein. Tr. at 91-92; 105-107. But even if this is true from a broad scientific standpoint, for purposes of this claim it constitutes speculation that cannot be the basis for the finding that Petitioner has established preponderant evidence sufficient to meet her burden of proof. *See, e.g., Snowbank Enter.*, 6 Cl. Ct. at 486 (speculation is insufficient under the preponderant evidence standard). A theory that depends in part on a finding of the presence of one kind of specific autoantibody

All in all, Petitioner could not establish that the course of her RA is consistent with her causation theory (beyond the fact that her RA began post-vaccination). As a treater, Dr. Middleton was qualified to offer a reading of the medical record consistent with Petitioner's theory, by highlighting aspects of it that showed Petitioner's causation theory occurring in real time. Instead, he expressly disavowed the ability to do so at all, confirming his view at trial that the most significant evidence he could identify as supporting the theory was the temporal relationship between vaccination and injury. Tr. at 105 ("On the 'did cause' part of the case that I have to decide, we have to rely upon the timing predominantly, right? A: Um-hum. Q: Yes? A. Correct"). It is a long-settled matter in the Program that this is an insufficient basis for an entitlement award. *Grant*, 956 F.2d at 1148. I cannot find on the basis of this medical record that the HPV vaccine more likely than not was the cause of Petitioner's RA – and indeed, cannot even pinpoint evidence supporting *what* its most likely cause was, given the total absence of any of the biomarkers/antibodies most associated with the disorder.

C. *Althen* Prong Three

As briefly noted above, Mrs. Olson persuasively testified that onset of her obvious RA-related symptoms began manifesting within one to two weeks of her receipt of the HPV vaccine in July 2010. But this temporal relationship is not enough for me to conclude that the third *Althen* prong has been satisfied.

First, because of the close relationship between the first and third *Althen* prongs, petitioners are obligated to establish that the timing of onset of symptoms is "medically appropriate" under their proposed causation theory. *See, e.g., de Bazan*, 539 F.3d at 1352 (the explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement)); *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013). But I have not found that Petitioner met her first *Althen* prong burden, because I do not find her theory – that alum in the HPV vaccine is alone sufficient to trigger RA in a person susceptible to the condition, and pursuant to the mechanism proposed in this case – to be scientifically or medically reliable. Accordingly, it does not matter that onset of the first obvious symptoms of Mrs. Olson's RA was temporally consistent with a theory that *itself* is not scientifically or medically reliable. *Caves v. Sec'y of Health & Human Servs.*, No. 07-443V, 2010 WL 5557542, at *22 (Fed. Cl. Spec. Mstr. Nov. 29, 2010) (a finding of an appropriate temporal relationship is insufficient to show causation-in-fact, as the other two prongs must *also* be met).

cannot evade the absence of such proof by proposing that *some other* autoantibody not yet identified by medical science is also likely to be present instead.

Second, that aspect of Petitioner's theory relying on an association between RA and individuals with chronic lung infections or like conditions, like Mrs. Olson, actually allowed for the possibility that her RA might have *preceded* vaccination – that it might already have been triggered independent of the HPV vaccine. Petitioner's theory that a vaccine could possibly act as an environmental trigger in a person susceptible to RA relied heavily on science involving the citrullination process initiating in the lung. *See, e.g.,* Sofat at 3; Ytterberg at 13. Such science establishes that an individual can possess the citrullinated antibodies that lead to the ECM protein destruction reflected in RA's primary symptoms long before clinical evidence of those symptoms manifests. Sofat at 2; van de Sande at 1. Indeed, Petitioner made a point of discussing the existence of a synovial subclinical period in which ACPAs (or some still-unidentified autoantibodies) would begin to perform their damaging, cross-reactive functions, even though outward clinical proof of RA (joint pain, visual swelling in joints) is lacking. Tr. at 49-51. And Dr. Middleton forthrightly admitted that he could not rule out all of the above starting before the HPV vaccine was administered. Tr. at 108.

CONCLUSION

Petitioner has unquestionably suffered from her RA, and I conclude from observing her at hearing that she is a truthful individual seeking a logical explanation for what caused her condition. Given the facts, I do not find it surprising that she and her experts deemed significant the fact that onset of her RA symptoms came after she received the HPV vaccine. The Vaccine Act, however, places far less stock in a mere temporal association. It permits me to award compensation only if a petitioner alleging a "non-Table Injury" can show by medical records or competent medical opinion that the injury was more likely than not vaccine-caused. Here, the weight of the evidence does not support Petitioner's causation theory, and there is insufficient evidence in the record that could be cited to show her theory working out as expected in real time, leaving me no choice but to hereby **DISMISS** this claim.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accord with this decision.[27]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[27] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.