In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 18-1350V
Filed: March 27, 2026

SHERRILL COTE, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner.
Lauren Kells, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On September 4, 2018, petitioner, Sherrill Cote, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa, *et seq.* (2012),[2] alleging that she suffers rheumatoid arthritis ("RA") resulting from the hepatitis B and/or influenza ("flu") vaccinations she received on May 10, 2016. (ECF Nos. 1, 48.) For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious or long-standing injury; and has

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa–10, *et seq.*

received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury.

In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1); § 300aa-11(c)(1)(C)(i); § 300aa-14(a).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines ex rel. Sevier v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

In this case, petitioner has alleged that hepatitis B and/or flu vaccines caused her to suffer rheumatoid arthritis. Because the alleged injury is not listed on the Vaccine Injury Table relative to either vaccine, petitioner must demonstrate causation-in-fact.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1278-79; *Hines*, 940 F.2d at 1525. Under that standard, petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. She need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition at issue and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278 (quoting *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992)). Ultimately, petitioner must satisfy what has come to be known as the *Althen* test, which requires: (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. *Id*.

A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1). Medical records are generally viewed as particularly trustworthy evidence because 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. § 300aa-13(b)(1). A petitioner may rely upon circumstantial evidence. *See Althen*, 418 F.3d at 1280. Moreover, the *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. While scientific certainty is not required, that expert's opinion must be based on "sound and reliable" medical or scientific explanation. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019).

Cases in the Vaccine Program are assigned to special masters who are responsible for "conducting all proceedings, including taking such evidence as may be appropriate, making the requisite findings of fact and conclusions of law, preparing a decision, and determining the amount of compensation, if any, to be awarded." Vaccine Rule 3(b)(1). Special masters must ensure each party has had a "full and fair opportunity" to develop the record but are empowered to determine the format for taking evidence based on the circumstances of each case, including having the discretion to decide cases without an evidentiary hearing. Vaccine Rule 3(b)(2); Vaccine Rule 8(a); Vaccine Rule 8(d). Special masters are not bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence in keeping with fundamental fairness to both parties. Vaccine Rule 8(b)(1). 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." § 300aa-13(b)(1). The special master is required to consider the entirety of the evidentiary record, draw plausible inferences, and articulate a rational basis for the decision. *Winkler v. Sec'y of Health & Human Servs.*, 88 F.4th 958, 963 (Fed. Cir. 2023) (citing *Hines*, 940 F.2d at 1528).

II. Procedural History

This case was initially assigned to another special master. (ECF No. 4.) In October and November of 2018, petitioner filed medical records and an affidavit. (ECF Nos. 8, 11; Exs. 1-4.) Thereafter, respondent filed a Rule 4(c) Report recommending against compensation and accompanied by a motion to dismiss in August of 2019. (ECF Nos. 24-25.) In addition to challenging causation-in-fact in the Rule 4(c) Report, respondent's motion to dismiss argued that petitioner had not shown that she satisfied the Vaccine Act's severity requirement (§ 300aa-11(c)(1)(D)(i)). (ECF No. 25.)

However, respondent's motion was denied in July of 2020 (ECF No. 29), after petitioner filed additional medical records (ECF No. 27; Exs. 5-6).

In January of 2021, petitioner filed an expert report by rheumatologist and immunologist M. Eric Gershwin, M.D. (ECF No. 33; Ex. 7), and respondent filed a responsive expert report by rheumatologist Christopher A. Mecoli, M.D., M.H.S. (ECF No. 36; Ex. A) in July of that year. In the following months, the parties exchanged another round of expert reports by Drs. Gershwin and Mecoli. (ECF Nos. 37-38; Exs. 13, C.) Thereafter, the parties advised that they would not file further expert reports and requested the case be resolved via a ruling on the written record.

On June 24, 2024, petitioner filed a motion for ruling on the written record. (ECF No. 48.) However, that motion was accompanied by a report from a new expert, immunologist Omid Akbari, Ph.D. (ECF Nos. 48-52; Ex. 14.) On November 8, 2024, respondent filed his response to petitioner's motion, as well as an expert report by immunologist John T. Bates, Ph.D., and a supplemental expert report by Dr. Mecoli. (ECF Nos. 55-56; Exs. D, F.) In December of 2024, petitioner filed her reply, as well as a supplemental expert report by Dr. Akbari. (ECF Nos. 59-61; Ex. 49.) Following this filing, respondent requested an opportunity to submit a sur-reply and supplemental expert reports responding to Dr. Akbari's most recent report. (ECF No. 62.)

Respondent's request for a sur-reply was granted by the special master presiding at the time; however, the case was then reassigned to the undersigned in February of 2025. (ECF Nos. 64-65.) Thereafter, respondent filed a sur-reply and a supplemental expert report by Dr. Bates. (ECF Nos. 66-67; Ex. H.) I then provided the parties the opportunity to confirm that the case is ripe for resolution of entitlement, which they did in a joint status report filed on April 2, 2025 (ECF No. 68), after which petitioner later filed updated medical records (ECF No. 69; Ex. 66).

In light of the above, I have determined that the parties have had a full and fair opportunity to develop the record and that it is appropriate to rule on the existing record. *See* Vaccine Rule 8(d); Vaccine Rule 3(b)(2); *Kreizenbeck v. Sec'y of Health & Human Servs.*, 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record"). Accordingly, petitioner's motion is now ripe for resolution.

III. Factual History

a. As reflected in the medical records

Petitioner, then fifty-five years of age, received the subject flu and hepatitis B vaccines on May 10, 2016, as part of a pre-employment physical examination. (Ex. 2, pp. 6-7.) She did not report any concerns apart from initially declining the flu vaccine due to a history of "dry heaves after previous flu shots." (*Id.* at 6.) However, during this encounter, she received the flu vaccine in her left deltoid and the hepatitis B vaccine in

her right deltoid. (*Id.* at 6-7.) Around the time of vaccination, petitioner was described as a "[l]ight tobacco smoker- less than 1/2 a pack per day." (Ex. 1, p. 3.)

On May 13, 2016, petitioner presented to the emergency department with a three-week history of cold symptoms, including headache, fever, chills, sweats, chest pain, cough, sore throat, and dyspnea. (Ex. 1, p. 3.) An x-ray of petitioner's chest was normal except for a slightly enlarged heart. (*Id.* at 4.) Based on her history and x-ray results, petitioner was believed to have pneumonia. (*Id.* at 4.) She was prescribed Zithromax, an antibiotic, and Phenergan with codeine, which combines an antihistamine with an opioid, before being discharged in stable condition. (*Id.* at 4-5.)

On June 20, 2016, petitioner presented for a workers' compensation evaluation during which she reported a three-day history of joint pain as potentially work-related. (Ex. 2, pp. 9-10.) Specifically, petitioner reported that she had been working at a new job for about a week, but "after 4 days she started with pain in her right wrist, shoulder, upper back, right clavicle and ankle and knee." (*Id.* at 9.) A physical exam showed tenderness to palpation over the right sternoclavicular joint with some slight swelling but no redness; tenderness in the right trapezius muscle; poor range of motion in the right shoulder but no swelling; and tenderness to palpation diffusely over the right wrist with moderate swelling. (*Id.*) Petitioner was diagnosed with unspecified joint pain, but her assessment was listed as "[d]iffuse arthralgias and inflammatory disorder of [the] right wrist." (*Id.* at 10.) She was prescribed a wrist splint and naproxen, and she was referred to rheumatology for further evaluation. (*Id.*) Petitioner's symptoms were believed to be unrelated to her work. (*Id.*)

On June 23, 2016, petitioner presented to her primary care provider with complaints of neck and back ache that reportedly began on May 14, 2016. (Ex. 1, p. 8.) Petitioner explained that

> [s]he started a new job, that she describes as being very physically active, on Monday May 13. The next morning she awoke with stiffness of her neck and shoulders that she describes as being unchanged from onset until now . . . She continued to work the rest of that week, then quit her job. She also describes intermittent joint pain in shoulder joints, elbows, wrists, hips, knees, and ankles. She describes this pain as being a 1-2 out of 10, sharp, and occurs with exertion lasting a few seconds only. She reports intermittent aching of her neck and knees that is mild and unchanged over the last few years. She describes having been seen . . . for her neck and shoulder pain on 6/20/16 and was prescribed naproxen which she has taken with partial relief, her only alleviating factor.

(*Id.*) Petitioner denied erythema or edema of the joints, any history of similar polyarthralgias, or that her symptoms interfered with her activities of daily living. (*Id.*) She also reported no familial history of rheumatologic disease. (*Id.*) On physical exam, petitioner had full range of motion of her bilateral shoulders. (*Id.* at 11.) She had some tightness of the bilateral cervical paraspinals and trapezius muscles as well as some

slight tenderness to palpation. (*Id*.) "She continued to complain of an intermittent vague ache, without localization, giving severity [of] 0-1/10 during . . . manipulation." (*Id*.) Her primary care provider could not exacerbate petitioner's symptoms on exam, and when her provider offered to examine any other joints that may be bothering her, petitioner stated "she had no other joint pain now." (*Id*.) At this time, petitioner's primary care provider was "unable to find any clear indication of a specific injury." (*Id.* at 8.)

She returned to her primary care provider the following day, on June 24, 2016. (Ex. 1, p. 14.) During this appointment, petitioner reported swelling in the right wrist and left knee, pain in the elbow, and fatigue, which had been "[g]oing on for about a week" and "[s]tarted after she began a new job working at a linen company doing a lot of standing and lifting." (*Id.*) A physical exam confirmed petitioner's reports of swelling in the left knee and right wrist, as well as generalized elbow pain. (*Id.* at 15.) However, her right wrist swelling extended into her forearm and was associated with pain on palpation. (*Id*.) Petitioner rated her "body aches" as an 8 out of 10. (*Id*.) It was suggested that petitioner's symptoms could have been related to "overuse of some sort of inflammatory process." (*Id.* at 14.) She was diagnosed with joint pain and started on a prednisone taper.[3] (*Id.* at 12-14.)

Petitioner's lab work of June 24, 2016, showed positive rheumatoid factor, elevated anti-cyclic citrullinated peptide (anti-CCP) of 140 units (reference range of <20 units), and elevated erythrocyte sedimentation rate (ESR) of 46 mm/hr (reference range of 0-15 mm/hr). (Ex. 1, pp. 17-25.) It was noted that a positive rheumatoid factor is "not diagnostic of rheumatoid but makes the [diagnosis] a possibility." (*Id.* at 21.) Based on the petitioner's positive rheumatoid factor and anti-CCP results, it was noted that she could have rheumatoid arthritis (RA). (*Id.* at 17.) Petitioner's modest elevation in ESR provided potential evidence of a nonspecific inflammatory process. (*Id.* at 18.) Petitioner also tested negative for Lyme and Hepatitis C antibodies. (*Id.* at 19, 22.)

On June 30, 2016, petitioner returned to her primary care provider for a follow up evaluation of her arthralgias. (Ex. 1, p. 26.) She reported that, on June 24, 2016, she awoke with significant worsening of her neck, shoulder, and wrist pain, as well as worsening edema in her right wrist and left knee and some erythema. (*Id.*) She experienced significant improvement in her symptoms after starting prednisone. (*Id*.) By this appointment, petitioner was reporting only "residual discomfort in her right wrist, shoulders, and neck" without edema. (*Id.* at 26-27.) On physical exam, petitioner had "partial range of motion in her right wrist, limited by discomfort, which she reports is significantly improved." (*Id.* at 27.) Her primary care provider diagnosed petitioner with polyarthralgia with edema and noted concern for rheumatologic disease, given that her blood work showed positive rheumatoid factor and elevated ESR rate. (*Id.* at 26.) Her provider also noted her daily smoking habit and "discussed the necessity for her to stop smoking particularly given her current complaints." (*Id*.) Petitioner stated that she was

[3] Prednisone is an orally administered synthetic glucocorticoid that is used as an anti-inflammatory and immunosuppressant in a wide variety of disorders. *Prednisone*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=40742 (last visited Jan. 29, 2026).

"not yet ready to quit" smoking at this time. (*Id*.) Her primary care provider emphasized the importance of a rheumatology consultation for determining a clear workup and plan of care. (*Id*.)

On July 23, 2016, petitioner returned to her primary care provider, reporting severe pain since discontinuing her prednisone taper. (Ex. 1, p. 29.) A physical exam revealed pain in the right wrist, as well as "swelling and deformity of the fingers consistent with arthritic inflammation." (*Id.* at 30.) After noting her positive anti-CCP and rheumatoid factor, her primary care provider assessed: "[m]ost likely new diagnosis of rheumatoid arthritis." (*Id.* at 29.) Petitioner was temporarily restated on a prednisone taper to relieve some of her discomfort. (*Id.* at 29, 31-32.)

Petitioner presented for a rheumatology evaluation by Todd Daugherty, M.D., on September 2, 2016. (Ex. 1, pp. 33, 39.) Dr. Daugherty recorded that petitioner had not experienced any joint symptoms "until 2 weeks after flu and Hep B vaccine[s] on 5/10/2016." (*Id.* at 39, 42.) Her symptoms began with wrist stiffness "in the first week of her job," followed by severe knee swelling. (*Id.* at 39.) Her fingers were later involved, and she had to quit her job in July due to her symptoms. (*Id.* at 39, 42.) About two weeks prior to this encounter, petitioner began to experience symptoms in her feet. (*Id*.) Although petitioner experienced some relief following her first prednisone taper, she reported that she was still experiencing severe symptoms since restarting prednisone in July. (*Id.* at 39.) On physical exam, petitioner had tenderness and severe swelling of the right wrist; tenderness of the right 1st metacarpophalangeal joint; tenderness and swelling of the left 1st metacarpophalangeal joint and 1st proximal interphalangeal joint; tenderness, swelling, and increased warmth of the left knee; tenderness and swelling of the right 2nd through 4th metatarsophalangeal joints; and severe diffuse swelling and tenderness of the left metatarsophalangeal joints. (*Id.* at 42.) Petitioner's lab work was negative for hepatitis B surface antigen and later also for M. tuberculosis complex. (*Id.* at 38; Ex. 3, p. 8.) It was noted that petitioner's mother has arthritis, but petitioner otherwise has no familial history of rheumatologic disease. (Ex. 1, p. 40.) Petitioner was diagnosed with "[s]evere new onset rheumatoid arthritis." (*Id.* at 42.) Her prednisone prescription was increased, and she was started on methotrexate.[4] (*Id.* at 33, 42, 50-51.)

On November 3, 2016, petitioner returned for a follow up rheumatology evaluation, which documented a diagnosis of Raynaud's disease. (Ex. 1, p. 55; *see also* Ex. 3, pp. 1-2, 5, 10.) At this time, petitioner's methotrexate prescription was increased, and she was placed on another prednisone taper. (Ex. 1, p. 55.) Petitioner was urged to quit smoking as smoking decreases the efficacy of methotrexate and "is a risk factor for rheumatoid arthritis." (*Id.*)

Petitioner's next encounter was not until August 3, 2017. (Ex. 5, p. 18.) During this primary care evaluation, petitioner reported that she had been sick for the past

[4] Methotrexate is used in the treatment of, *inter alia*, severe rheumatoid arthritis. *Methotrexate*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=30930 (last visited Jan. 29, 2026).

couple of weeks. (*Id.*) Her physical exam was unremarkable, and she was assessed with acute sinusitis. (*Id*.) Almost two weeks later, petitioner returned for a rheumatology evaluation on August 14, 2017. (*Id.* at 4.) Petitioner reported that she had been off prednisone for a few months, and she continued to have pain in her feet, wrists, and fingers, as well as swelling in her feet and left knee. (*Id*.) It was noted that, since her last rheumatology evaluation, petitioner had stopped taking methotrexate in January of 2017 "due to poor response," that she was then started on Leflunomide[5] but she discontinued in March of 2017 due to hair loss, that she was started on Xeljanz[6] in late March or April of 2017, and that she was restarted on methotrexate in August of 2017. (*Id.* at 5.) On physical exam, petitioner had tenderness in the left ankle and diffuse metatarsophalangeal joints. (*Id.* at 7.) Dr. Daugherty's assessment was seropositive RA. (*Id*.) It was noted that petitioner had experienced a good but incomplete response to Xeljanz and that she had much less swelling and tenderness on exam, despite being off prednisone. (*Id.*) Because petitioner had some response to methotrexate but experienced nausea with the higher dose, Dr. Daugherty prescribed a low dose methotrexate to be taken in combination with Xeljanz. (*Id.*) Dr. Daugherty opined that petitioner's Raynaud's disease was related to her RA and smoking. (*Id.* at 8.) Petitioner was again encouraged to limit her smoking because smoking decreases the efficacy of the RA treatment and worsens Raynaud's disease. (*Id*.)

In October of 2017, petitioner returned to her primary care provider with a one-week history of acute sinusitis associated with hoarseness and postnasal drip. (Ex. 5, p. 1.) Petitioner had no other complaints, and only Xeljanz was listed under her relevant current medications. (*Id.* at 1-2.) Several months later, in May of 2018, petitioner returned to her primary care provider with a one-month history of sinusitis and otalgia. (*Id.* at 20-21.) Her symptoms were associated with congestion, ear pain, a plugged ear sensation, sinus pain, earache, and sore throat. (*Id.* at 20.) Petitioner had no other musculoskeletal complaints, and she was diagnosed with acute non-recurrent maxillary sinusitis. (*Id.* at 21.) Petitioner returned to her primary provider in September of 2018 with reports of a four-month history of hoarseness, bilateral maxillary pain, and left-sided otalgia. (*Id.* at 21-22.) She had no other musculoskeletal complaints at this time. (*Id.* at 21-23.)

On January 25, 2019, petitioner returned for a rheumatology evaluation of her seropositive RA. (Ex. 6, p. 1.) It was noted that petitioner was still taking Xeljanz but that she discontinued sulfasalazine, which she had started taking in August of 2017,[7]

[5] Leflunomide is an orally administered disease-modifying antirheumatic drug that is used in the treatment of RA. *Leflunomide*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=27821 (last visited Jan. 29, 2026).

[6] Xeljanz, the trademark preparation of tofacitinib citrate, is used in the treatment of RA. *Xeljanz*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=137176 (last visited Jan. 29, 2026).

[7] Sulfasalazine is an orally administered disease-modifying anti-rheumatic drug that is used in the treatment of RA. *Sulfasalazine*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=47968 (last visited Jan. 29, 2026).

due to nausea. (*Id.* at 1, 4; *see also* Ex. 6, p. 2.) However, her joint symptoms reportedly worsened. (Ex. 6, pp. 1, 4.) She stated that she was willing to restart methotrexate in combination with Xeljanz. (*Id.* at 1.) It was also noted that petitioner continued to smoke about 10 cigarettes per day but that she was trying to cut back. (*Id.* at 1, 5.) Petitioner reported that her joint symptoms were aggravated by the cold weather and shoveling snow. (*Id.* at 1.) She reported pain in the elbow, wrist, and shoulder, as well as swelling in the right wrist and left knee. (*Id*.) Her Raynaud's was noted to be associated with mild purplish changes. (*Id*.) She also reported fatigue and paresthesia in her hands and feet. (*Id*.) On physical exam, petitioner had tenderness over her left diffuse metatarsophalangeal joint, right 1st metatarsophalangeal joint, bilateral ankles, left 1st metacarpophalangeal joint, and right metacarpophalangeal joint with the exception of the 4th metacarpophalangeal joint. (*Id.* at 3.) Dr. Daugherty continued to assess seropositive RA, but he specified that her remaining tenderness was "much improved from baseline." (*Id.* at 4.) It was noted that petitioner's recent labs showed "mildly elevated [C-reactive protein] and ESR which correlates with moderate but incomplete response to Xeljanz monotherapy" and that "monitoring labs were normal." (*Id.* at 4-5.) However, Dr. Daugherty noted that petitioner had associated paresthesia and fatigue, as well as mild Raynaud's. (*Id.* at 4.)

In May of 2019, petitioner returned for a follow up rheumatology evaluation by Dr. Daugherty. (Ex. 6, p. 8.) She reported cramping in her feet; paresthesia in her hands and feet; pain in her hands, wrists, elbows, shoulders, feet, ankles, and knees; swelling in her wrists, elbows, and knees; moderate eye dryness; severe mouth dryness; and fatigue. (*Id*.) She reported that she was still smoking and that she held off on taking Xeljanz while she had walking pneumonia. (*Id.*) She reported a "moderate/good response" to Xeljanz and sulfasalazine, but she had not started methotrexate because she could not manipulate the syringe due to numbness in her hands. (*Id.* at 8, 11.) Petitioner's methotrexate prescription was switched from injection to pill form and added to petitioner's treatment plan. (*Id.* at 11-12.) On physical exam, petitioner had mild left shoulder tenderness, mild right elbow tenderness, bilateral ankle tenderness, and tenderness and swelling in her bilateral metatarsophalangeal joints. (*Id.* at 10.) Dr. Daugherty noted that petitioner "has less tenderness and swelling on exam than baseline and her inflammatory markers have normalized and her physical function is improved." (*Id.* at 11.) Dr. Daugherty again emphasized "the role of smoking as an inflammatory trigger and that smoking decreases efficacy of [disease-modifying anti-rheumatic drugs] and that smoking cessation is an essential part of her treatment plan." (*Id*.)

Petitioner followed up with Dr. Daugherty in July of 2019. (Ex. 6, p. 13.) She reported that her symptoms were only partially controlled by her treatment with Xeljanz. (*Id*.) She continued to complain of paresthesia in her hands; stiffness in her knees, ankles, and feet; and swelling in her hands, wrists, feet, ankles, and knees. (*Id*.) She reported a "severe flare" of swelling after "a falling out with her nephew." (*Id*.) She also reported that her joint symptoms worsened after discontinuing sulfasalazine two weeks prior. (*Id*.) On physical exam, petitioner had mild bilateral wrist tenderness, left 1st metacarpophalangeal and proximal interphalangeal joint tenderness, right knee

tenderness, left ankle tenderness and swelling, and "[l]eft greater than right diffuse [metatarsophalangeal joint] tenderness and swelling and hammertoe deformities and left foot." (*Id.* at 15.) Dr. Daugherty noted that, at her last visit, petitioner "was having a moderate good response but still incomplete response to sulfasalazine and Xeljanz . . . We added methotrexate pill form to sulfasalazine and Xeljanz. We had wanted to start methotrexate injections since [they are] better tolerated and more effective but she preferred the pill form." (*Id.* at 15-16.) Petitioner had discontinued methotrexate and sulfasalazine due to increased nausea. (*Id.* at 13, 16.) Since then, petitioner had experienced increased joint symptoms, as well as fatigue and paresthesia. (*Id.* at 16.) However, Dr. Daugherty noted that, despite relatively more tenderness and swelling since discontinuing her treatment with sulfasalazine, petitioner was "clearly much better than baseline." (*Id*.) As for her Raynaud's, it was noted that her condition was more problematic in her feet in the warmer months and that she would benefit from ceasing to smoke. (*Id*.) Dr. Daugherty further noted that "[s]moking is a known risk factor for inflammatory activity and also decreases efficacy of [disease-modifying anti-rheumatic drugs] so at each visit we strongly encouraged her to quit smoking since this could have dramatic impact on her response to therapy." (*Id*.) Petitioner was restarted on sulfasalazine. (*Id.* at 16-17.)

Additionally, petitioner later filed updated medical records which document two further rheumatology encounters with a new rheumatologist, Yan Li, M.D. (Ex. 66.) The updated records indicate that petitioner's RA was relatively stable with low-dose sulfasalazine, Xeljanz, and prednisone as needed for flares. These records also confirm that petitioner remained an active smoker.

b. Affidavit

Petitioner filed an affidavit in support of her claim. (Ex. 4.) Petitioner avers that she received the subject flu and hepatitis B vaccinations at an urgent care center in New Hampshire on May 10, 2016. (*Id.* at ¶ 2.) She states that, within a few days of her vaccinations, she began to experience pain and swelling in her joints. (*Id.* at ¶ 3.) She returned to urgent care on May 20, 2016, for an evaluation of her pain and swelling, and she was referred to a rheumatologist for further evaluation. (*Id*.) Following testing, including blood work, petitioner was diagnosed with "new onset severe rheumatoid arthritis." (*Id.* at ¶ 4.) She avers that she continues to experience symptoms associated with RA, and she is still being treated for her condition. (*Id.* at ¶ 5.)

IV. Expert Opinions

a. Petitioner's Rheumatology and Immunology Expert, M. Eric Gershwin, M.D.[8]

Dr. Gershwin authored two expert reports on behalf of petitioner. (Exs. 7, 13.) Dr. Gershwin opines that the hepatitis B vaccine that petitioner received on May 10, 2016, caused her to suffer seropositive rheumatoid arthritis ("RA").[9] (Ex. 7.) Dr. Gershwin notes petitioner's relevant medical history as including abnormal lipids, a hysterectomy, a cholecystectomy, a slightly enlarged heart, trace right pleural effusion, and a more than 20-year history of smoking. (*Id.* at 1-2.) On May 13, 2016, just three days post-vaccination, petitioner reported a three-week history of respiratory infection with more recent onset of shortness of breath. (*Id.* at 1.) The following day, on May 14, 2016, petitioner began to notice stiffness of her neck and shoulders, along with intermittent polyarthralgias in her elbows, hips, knees, ankles, and wrists. (*Id.* at 1-2.) Thereafter, petitioner's sedimentation rate was measured at 46, and she was found to have a positive anti-CCP and rheumatoid factor. (*Id.* at 1.) Dr. Gershwin opines that petitioner was correctly diagnosed with seropositive RA, for which she was treated with anti-inflammatory agents and a Jak inhibitor. (*Id.* at 2.) He further acknowledges petitioner's concurrent diagnosis of Raynaud's disease. (*Id.*)

Dr. Gershwin explains that RA is a "classic" autoimmune disease, affecting up to 1% of women. (Ex. 7, p. 2.) He notes that smoking and genetics have been identified as potential risk factors for the development of RA, though he asserts that the epidemiology "has failed to provide a statistical degree of precision in such prediction." (*Id.* at 1-2, 6.) He also notes that respiratory infections have been associated with an increased risk of RA "in some people." (*Id.* at 1.) Dr. Gershwin explains "classic autoantibodies" found in RA, such as antibodies to CCP and rheumatoid factor, can be detected "years before the onset of clinical disease in some people." (*Id.* at 2.) Moreover, titers of RA-associated autoantibodies remain constant, despite variation in disease activity, and as a result, such autoantibodies are not routinely monitored as a

---

[8] Dr. Gershwin received his medical degree from Stanford University, before going on to complete an internship and residency at Tufts New England Medical Center. *Meyers v. Sec'y of Health & Human Servs.*, No. 19-272V, 2025 WL 2754664, at *12 n.14 (Fed. Cl. Spec. Mstr. Aug. 22, 2025). He is a Distinguished Professor of Medicine and Chief of Division of Rheumatology, Allergy and Clinical Immunology at the University of California School of Medicine at Davis, where he has been employed for over 40 years. (Ex. 7, p. 1.) Dr. Gershwin is board-certified in internal medicine with a subspecialty in rheumatology, as well as in allergy and clinical immunology, and he maintains an active medical license in California. *Meyers*, 2025 WL 2754664, at *12 n.14. In his research capacity, Dr. Gershwin has maintained a "long term research interest . . . in understanding the etiologies of autoimmune disease, including rheumatoid arthritis." (Ex. 7, p. 1.)

[9] Dr. Gershwin appears to also argue in the alternative that, "[i]f one were to considers [petitioner's] clinical course under an aggravation analysis, then it is clear that her RA was significantly worse after receipt of her Hep B vaccination." (Ex. 7, p. 7.) However, he opines that none of the symptoms associated with her RA were present prior to May 14, 2016, stating specifically that petitioner "did not develop clinical symptoms of RA until four days after her Hep B vaccination." (*Id.* at 1-2.) Petitioner has not alleged that the subject vaccinations significantly aggravated a preexisting condition.

biomarker of disease activity. (*Id.* at 6.) However, Dr. Gershwin opines that there is a difference between the etiologies that are responsible for disease induction and actual events that determine disease activity. (*Id.* at 5-6; Ex. 13, p. 3.) For example, patients with seropositive RA produce antibodies against citrullinated peptides, including vimentin, alpha enolase, and fibrinogen. (Ex. 7, p. 6; Ex. 13, p. 3.) Dr. Gershwin explains that we do not know why these specific peptides lead to synovitis and that antibodies to these peptides appear to peak regardless of the patient's clinical course. (Ex. 7, p. 6 (citing Nicola Bizzaro et al., *Anti-Cyclic Citrullinated Peptide Antibody Titer Predicts Time to Rheumatoid Arthritis Onset in Patients with Undifferentiated Arthritis: Results From a 2-Year Prospective Study*, 15 ARTHRITIS RSCH. & THERAPY 1 (2013) (Ex. 11)); Ex. 13, p. 3 (citing Bizzaro et al., *supra*, at Ex. 11).) Thus, Dr. Gershwin opines that "it is the immune response that dictates the events here and attempting retrospectively to identify the peptides involved is neither clinically nor scientifically possible." (Ex. 13, p. 1.)

Dr. Gershwin describes a "multi-step pathogenesis in autoimmunity," including "multiple inherited and somatic mutations which are required for loss of tolerance." (Ex. 7, p. 6 (citing Christopher C. Goodnow, *Multistep Pathogenesis of Autoimmune Disease*, 130 CELL 25 (2007) (Ex. 9)).) Additionally, Dr. Gershwin opines that a breaking of tolerance may be possible through "mechanisms of bystander activation, production of pro-inflammatory cytokines, alterations of nucleic acid sensors, . . . innate immunity and finally disruption of T and B regulatory pathways." (*Id*.) He suggests that "more than one of these pathways may be involved" and individuals with "a strong genetic predisposition may require fewer somatic events." (*Id*.) Dr. Gershwin summarizes his causal opinion as combining "the concept of somatic mutation and the contribution of cytokine driven events following vaccination to trigger a further somatic event, in this case, contributing to the clinical onset of rheumatoid arthritis." (Ex. 13, p. 1.)

In the instant case, Dr. Gershwin asserts that "we can assume that [petitioner] mostly likely has an underlying genetic susceptibility to develop RA." (Ex. 13, p. 3.) Dr. Gershwin opines that petitioner likely had pre-existing antibodies to CCP and positive rheumatoid factor as such antibodies can be present for years prior to onset of clinical disease; however, he acknowledges that testing to confirm whether petitioner had antibodies associated with RA was not performed prior to symptom onset. (Ex. 7, pp. 2, 6.) Moreover, while petitioner was asymptomatic prior to vaccination, Dr. Gershwin opines that, given her genetic predisposition, history of smoking, and ongoing respiratory infection, the hepatitis B vaccination of May 10, 2016, was likely "the final somatic event in the expression of clinical symptomatology." (*Id.* at 6.) Although Dr. Gershwin acknowledges the lack of epidemiology associating the hepatitis B vaccine with development of RA, he explains that epidemiology is not useful for capturing rare events. (*Id*.; Ex. 13, pp. 1-2.)

Finally, Dr. Gershwin opines that petitioner's four-day onset is "completely appropriate." (Ex. 7, p. 7.) He notes that the "onset of clinical symptomatology will be driven by the innate immune system, i.e. inflammation," which typically occurs within 24

hours post-vaccination. (*Id.* (citing Caroline Hervé et al., *The How's and What's of Vaccine Reactogenicity*, NPJ VACCINES, Sep. 24, 2019, at 1 (Ex. 12)).)

b. Petitioner's Immunology Expert, Omid Akbari, Ph.D.[10]

Dr. Akbari authored two expert reports on behalf of petitioner. (Exs. 14, 49.) Dr. Akbari opines that petitioner developed RA as a result of the hepatitis B and flu vaccines received on May 10, 2016. (Ex. 14, pp. 2, 23.) He describes her relevant pre-vaccination medical history as including kidney stones and smoking. (*Id.* at 3 (citing Ex. 1, pp. 3, 10).) He emphasizes that petitioner had no history of joint pain or arthralgias prior to the subject vaccinations. (*Id.* at 5.) He notes that, on May 13, 2016, petitioner presented with a three-week history of cold symptoms, and the following day, she presented with stiffness in her neck and shoulders, as well as intermittent polyarthralgia in her elbows, hips, knees, ankles, and wrists. (*Id.* at 3-4 (citing Ex. 1, p. 3).) She continued to complain of joint pain and swelling into June of 2016, when she was finally placed on prednisone and experienced some relief in her symptoms. (*Id.* at 4 (citing Ex. 1, p. 18; Ex. 2, pp. 9-10, 12, 14-15).) Subsequent blood work showed positive anti-CCP and rheumatoid factor, as well as elevated sedimentation rate, suggesting an inflammatory or autoimmune process. (*Id.* (citing Ex. 1, pp. 17-18, 21).) Following a rheumatology consultation, petitioner was diagnosed with "severe new onset rheumatoid arthritis" and prescribed methotrexate and folic acid with an increased steroid dose. (*Id.* at 4-5 (citing Ex. 1, pp. 38-39, 42).) Notably, blood work was, *inter alia*, negative for hepatitis B. (*Id.* at 5 (citing Ex. 1, p. 38).)

Dr. Akbari describes RA as an inflammatory autoimmune disease and explains that the joint inflammation that is characteristic of RA is "closely related to infiltration of immune cells and secretion of proinflammatory cytokines, which lead to cartilage degradation and bone erosion." (Ex. 14, p. 5.) Immune cells, such as monocytes/macrophages and T cells,[11] appear in the joints of patients with RA. (*Id.*)

[10] Dr. Akbari received his Ph.D. in cellular and molecular immunology from the University of London in 1998, before going on to complete a post-doctoral fellowship at Stanford University in 2001. (Ex. 48, p. 1.) He maintains a position as a professor of immunology at the University of Southern California, Los Angeles. (*Id.* at 2.) Prior to that, he worked as a senior scientist in the Division of Allergy and Immunology at Stanford University and an assistant professor of pediatrics in the Division of Immunology at Harvard Medical School. (*Id.*) Dr. Akbari has studied the murine and human immune systems for over 20 years with a focus on the role of immune tolerance and how immune cells induce autoimmune and allergic diseases. (Ex. 14, p. 2.) Pertinent here, Dr. Akbari's research "involves investigating and characterizing the mechanisms underlying the regulation of the acquired and innate immune responses," including multiple research studies related to "how an antigen, allergen or a vaccine can result in an appropriate or dysregulated immune response and inflammation." (*Id.* at 3.) He has authored 123 publications. (Ex. 48, pp. 15-33.)

[11] Dr. Akbari explains that there were two types of CD4+ T cells at play: regulatory T cells ("Treg") and effector T cells ("Teff"). (Ex. 14, pp. 13-14.) CD4+ (helper) T cells are T lymphocytes that are primarily responsible for cell-mediated immunity and carry the CD4 antigen, which is used to distinguish cell lineages, developmental stages, and functional subsets. *CD4 cells*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=63999 (last visited Jan. 27, 2026); *T lymphocytes*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=87562 (last visited Jan. 27, 2026); *CD antigen*,

Monocytes/macrophages are antigen presenting cells that function to recruit and promote the differentiation of T cells into inflammatory phenotypes. (*Id.*; Ex. 49, p. 5.) At the same time, different subtypes of T cells can recruit monocytes/macrophages and promote osteoblast differentiation and production of inflammatory cytokines. (Ex. 14, p. 5.) One such T helper cell is Th17, which secretes interleukin (IL)-17, a molecule that induces inflammation and plays a role in generating effective long-lived vaccine-induced immunity against viruses. (*Id.* at 5, 11 (citing José Francisco Zambrano-Zaragoza et al., *Th17 Cells in Autoimmune and Infectious Diseases*, INT'L J. INFLAMMATION, 2014, at 1 (Ex. 15)).) Dr. Akbari opines that Th17 is involved in the pathogenesis of various autoimmune diseases, including RA. (*Id.* (citing Zambrano-Zaragoza et al., *supra*, at Ex. 15).) He explains that, in the early stages of RA, M1-polarized macrophages secrete high levels of IL-6 and IL-23, and that these M1 cytokines favor the differentiation of naïve T cells into Th17 cells. (*Id.* at 5.) Th17-produced cytokine profiles, including IL-17 and tumor necrosis factor (TNF)-α, have proinflammatory functions, which suggests that such profiles may be "an important factor in immune-pathogenesis of RA." (*Id.*) Studies have shown that patients with RA have increased levels of Th17 cells in their peripheral blood and joints, and that patients who have been infected with or vaccinated against flu have elevated levels of IL-17. (*Id.* at 5, 11 (citing Paul J. Egan et al., *Promotion of the Local Differentiation of Murine Th17 Cells by Synovial Macrophages During Acute Inflammatory Arthritis*, 58 ARTHRITIS & RHEUMATISM 3720 (2008) (Ex. 16); Jesus F. Bermejo-Martin et al., *Th1 and Th17 Hypercytokinemia as Early Host Response Signature in Severe Pandemic Influenza*, 13 CRITICAL CARE 1 (2009) (Ex. 29); Yinyao Lin et al., *Th17 Cytokines and Vaccine-Induced Immunity*, 32 SEMINARS IMMUNOPATHOLOGY 79 (2010) (Ex. 30)).)

Dr. Akbari goes on to assert that vaccine-induced inflammasomes, including NLRP3 inflammasome, "play an important role as [an] initial trigger for the development of RA." (Ex. 14, p. 7 (citing Hui Yin et al., *Role of NLR3 Inflammasome in Rheumatoid Arthritis*, 13 FRONTIERS IMMUNOLOGY 1 (2022) (Exs. 21, 57)); Ex. 49, p. 7.) Dr. Akbari explains that inflammasomes consist of three primary components: a pattern recognition receptor, an adaptor protein, and an effector molecule called caspase-1. (Ex. 49, p. 6.)

DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=56883 (last visited Jan. 27, 2026). Regulatory T cells "play a crucial role in maintaining the delicate balance that helps prevent the development of autoimmune disorders." (Ex. 49, p. 10.) These regulatory T cells actively suppress the immune system by secreting cytokines that regulate the activation and effector functions of autopathogenic T cells and suppress other immune cells, such as B cells, T cells, dendritic cells, and macrophages. (Ex. 14, p. 6 (citing Chi-Mou Juang et al., *Regulatory T Cells: Potential Target in Anticancer Immunotherapy*, 46 TAIWAN J. OBSTETRICS & GYNECOLOGY 215 (2007) (Ex. 17)).) Following the resolution of the inflammatory response, activated regulatory T cells persist in the targeted tissue, "ready to attenuate subsequent autoimmune reactions upon re-expression of the antigen." (Ex. 49, p. 10.) However, immune provocations, such as infection or vaccination, also stimulate effector T cells, such as Th17 cells, which are pathogenic. (Ex. 14, pp. 11, 14.) Dr. Akbari explains that alteration of the suppressive function of regulatory T cells has been associated with induction/severity of autoimmune disease, and a decrease in the number of regulatory T cells "most likely is a main factor resulting in a person's predisposition to develop autoimmune disease during activation of the immune system." (*Id.* at 6.) Thus, immune homeostasis depends on maintaining a balance between regulatory T cells and effector T cells. (*Id.* at 11, 14.)

Vaccine antigens, such as the hepatitis B surface antigen, trigger the activation of pattern recognition receptors (e.g., toll-like receptors (TLRs), NOD-like receptors (NLRs)), which recognize pathogen- and danger-associated molecular patterns (PAMPs/DAMPs), leading to further activation of downstream signaling pathways that involve NF-κB. (Ex. 14, pp. 10-11 (citing Kiyoshi Takeda et al., *Toll-Like Receptors*, 21 ANNUAL REV. IMMUNOLOGY 335 (2003) (Ex. 26); Alexander Khoruts et al., *IL-1 Acts on Antigen-Presenting Cells to Enhance the* In Vivo *Proliferation of Antigen-Stimulated Naïve CD4 T Cells Via a CD28-Dependent Mechanism That Does Not Involve Increased Expression of CD28 Ligands*, 34 EUR. J. IMMUNOLOGY 1085 (2004) (Ex. 27)); Ex. 49, p. 6.) NF-κB is a transcription factor that promotes the expression of pro-inflammatory cytokines, such as pro-IL-1β, and components of the inflammasome itself, such as NLRP3. (Ex. 14, p. 10.) Pattern recognition receptors also recognize alum (*Id.* at 9), leading to the release of DAMPs and further activating NLRP3 inflammasome (*Id.* at 10). Once activated, NLRP3 oligomerizes and recruits the adaptor protein, which then recruits and activates caspase-1. (*Id.*; Ex. 49, pp. 6-7.) Activated caspase-1 processes and secretes IL-1β and IL-18, which are cytokines that contribute to the local inflammatory response and promote the recruitment and activation of other immune cells to the vaccination site. (Ex. 14, pp. 10-11 (citing Virginie Pétrilli et al., *The Inflammasome: A Danger Sensing Complex Triggering Innate Immunity*, 19 CURRENT OP. IMMUNOLOGY 615 (2007) (Ex. 28)); Ex. 49, pp. 6-7.)

Dr. Akbari explains that inflammasome activation enhances the immune response to the vaccine antigen and aids in the generation of specific antibodies and memory cells against the virus. (Ex. 14, p. 10; Ex. 49, p. 3 (noting that "it is a widely acknowledged concept among immunologists that the induction of inflammasomes and cytokines, such as IL-1, is crucial for eliciting a protective immune response in individuals who receive vaccinations").) Crooke et al. demonstrates that flu vaccination triggers inflammasome activation and subsequent production of IL-1. (Ex. 14, pp. 7-8 (citing Stephen N. Crooke et al., *Inflammasome Activity in Response to Influenza Vaccination Is Maintained in Monocyte-Derived Peripheral Blood Macrophages in Older Adults*, 2 FRONTIERS AGING 1 (2021) (Exs. 22, 51)); *see also* Pin Wan et al., *AP-1 Signaling Pathway Promotes Pro-IL-1β Transcription to Facilitate NLRP3 Inflammasome Activation Upon Influenza A Virus Infection*, 13 VIRULENCE 502 (2022) (Ex. 23).) These findings were confirmed in a subsequent study, in which Fourati et al. identify a high inflammatory (inflam.hi) endotype that represented high levels of inflammasome among flu and other vaccine recipients. (Ex. 49, p. 4 (citing Slim Fourati et al., *Pan-Vaccine Analysis Reveals Innate Immune Endotypes Predictive of Antibody Responses to Vaccination*, 23 NATURE IMMUNOLOGY 1777 (2022) (Ex. 55)).) The study observed that the NF-κB pathway and its target genes, including pro-inflammatory cytokines (TNF, IL-6, IL-1β) and their receptors or effector molecules regulated by NF-κB, were all elevated in this endotype. (*Id.* at 5 (citing Fourati et al., *supra*, at Ex. 55).) Moreover, several genes of the inflammasome complex and IL-1 signaling were also upregulated. (*Id.* (citing Fourati et al., *supra*, at Ex. 55).) This data was further confirmed by a study by Hagan et al. that "published the results of transcriptional factors signature in a cluster of patients after immunization." (*Id.* (citing Thomas Hagan et al., *Transcriptional Atlas of the Human Immune Response to 13 Vaccines Reveals a*

Common Predictor of Vaccine-Induced Antibody Responses, 23 NATURE IMMUNOLOGY 1788 (2022) (Ex. 56)).) Yang et al. showed that "viral proteins alone can trigger inflammasome" by activating NLRP1 inflammasome directly. (Ex. 14, p. 8 (citing Xing Yang et al., *KSHV-Encoded ORF45 Activates Human NLRP1 Inflammasome*, 23 NATURE IMMUNOLOGY 916 (2022) (Ex. 24)).) Dr. Akbari explains that many of the viral components described by Hartenian & Broz are found in the flu vaccine received by petitioner. (*Id.* at 8-9 (citing Ella Hartenian & Petr Broz, *Viral Protein Activates the NLRP1 Inflammasome*, 23 NATURE IMMUNOLOGY 822 (2022) (Ex. 25)).) He additionally opines that the hepatitis B vaccine can activate inflammasomes through the interaction of hepatitis B peptides, along with adjuvants like alum, and the immune system. (*Id.* at 9.) He notes that alum is "a potent activator of the immune system."[12] (*Id*.) Thus, Dr. Akbari opines that "inflammasome activation may be caused directly by the component of viruses, or indirectly via the products of cell damage induced by the material." (*Id.* at 11; *see also* Ex. 49, p. 5.)

Dr. Akbari illustrates the importance of inflammasomes in the pathogenesis of RA by citing several studies that highlight the following information:

> NLRP3 inflammasome [is] a major regulator of inflammation in RA, and act[s] as a primary source of pro-inflammatory cytokines IL-1 and IL-18. Elevated levels of inflammatory cytokines, including TNF, IL-6, and IL-1β, have been observed in RA sera compared to healthy controls. Additionally, upregulation of NLRP3 mRNA and associated proteins has been found in monocytes, macrophages, and dendritic cells of RA patients. Activation of the inflammasome and subsequent production of IL-1β also enhances the secretion of chemokines and cytokines, promotes Th17 cell differentiation, and reduces cartilage component synthesis, contributing to the pathogenesis of RA. Moreover, polymorphisms in inflammasome-related genes, such as NLRP3 and CARD8, have been associated with increased RA susceptibility and altered responses to anti-TNF treatments. Furthermore, elevated levels of caspase-1 and IL-18 in RA patients provide further evidence supporting the role of inflammasome activation in disease progression. The NLRP3 inflammasome has been shown to contribute to synovial inflammation, cartilage degeneration, and bone destruction, all hallmark features of RA. Together, these findings underline the critical involvement of inflammasomes and their related pathways in both the development and progression of rheumatoid arthritis.

[12] Notably, Dr. Akbari specifically states that he is not relying on the concept of autoimmune syndrome induced by adjuvants (ASIA). (Ex. 14, p. 9.) When presented in prior cases in the Vaccine Program, ASIA has been the subject of substantial criticism and has been repeatedly rejected as a viable theory on causation. *See J.F. v. Sec'y of Health & Human Servs.*, No. 13-799V, 2022 WL 5434214 (Fed. Cl. Spec. Mstr. Sep. 9, 2022); *D'Angiolini v. Sec'y of Health & Human Servs.*, No. 99-578V, 2014 WL 1678145 (Fed. Cl. Spec. Mstr. Mar. 27, 2014), *mot. for rev. denied*, 122 Fed. Cl. 86 (2015), *aff'd per curiam*, 645 F. App'x 1002 (Fed. Cir. 2016); *Rowan v. Sec'y of Health & Human Servs.*, No. 10-272V, 2014 WL 7465661 (Fed. Cl. Spec. Mstr. Dec. 8, 2014), *mot. for rev. denied*, No. 10-272V, 2015 WL 3562409 (Fed. Cl. May 18, 2015).

(Ex. 49, pp. 7-8 (citations omitted) (citing Hui Yin et al., *supra*, at Ex. 57; Qi Jiang et al., *Function and Role of Regulatory T Cells in Rheumatoid Arthritis*, 12 FRONTIERS IMMUNOLOGY 1 (2021) (Ex. 58); Rebeccah J. Mathews et al., *Evidence of NLRP3-Inflammasome Activation in Rheumatoid Arthritis (RA); Genetic Variants Within the NLRP3-Inflammasome Complex in Relation to Susceptibility to RA and Response to Anti-TNF Treatment*, 73 ANNALS RHEUMATIC DISEASES 1202 (2014) (Ex. 59)).) Accordingly, Dr. Akbari opines that "many studies including cohort and mechanistic studies, support the notion that induction of inflammasome[s] (IL-1 and IL-6) along with T cell stimulation, after administration of influenza and [hepatitis] B vaccine, are capable of triggering RA." (Ex. 14, p. 13.)

Dr. Akbari opines that RA has been associated with both the flu and hepatitis B vaccines. (Ex. 14, pp. 12-13; Ex. 49, pp. 12-13.) He cited a study by Symmons & Chakravarty, which found that approximately 5.3% (48 out of 898) of patients with early inflammatory polyarthritis reported either tetanus or flu vaccination within six-weeks of onset. (Ex. 14, p. 12 (citing D.P.M. Symmons & K. Chakravarty, *Can Immunisation Trigger Rheumatoid Arthritis?*, 52 ANNALS RHEUMATIC DISEASES 843 (1993) (Ex. 31)).) Dr. Akbari also cites a cohort study by Ray et al., which assessed the risk of RA following vaccination with tetanus, flu, and hepatitis B vaccines and found a possible temporal relationship between RA and immunization against flu and hepatitis B. (*Id.* (citing Paula Ray et al., *Risk of Rheumatoid Arthritis Following Vaccination with Tetanus, Influenza and Hepatitis B Vaccines Among Persons 15-59 Years of Age*, 29 VACCINE 6592 (2011) (Ex. 33)).) Additionally, there have been several case reports suggesting a temporal relationship between flu vaccination and RA. (*Id.* (citing Gurjot Basra et al., *Rheumatoid Arthritis and Swine Influenza Vaccine: A Case Report*, CASE REPS. RHEUMATOLOGY, 2012, at 1 (Ex. 32)).)

Regarding the hepatitis B vaccine, Dr. Akbari cites a study by Pope et al. that investigated the association between the hepatitis B vaccine and RA. (Ex. 14, p. 12 (citing Janet E. Pope et al., *The Development of Rheumatoid Arthritis After Recombinant Hepatitis B Vaccination*, 25 J. RHEUMATOLOGY 1687 (1998) (Exs. 34, 63)); Ex. 49, p. 12 (citing Pope et al., *supra*, at Ex. 63).) He explains that 10 out of 11 patients studied met the revised American College of Rheumatology criteria for RA and 5 subjects were HLA-DR4 positive. (Ex. 14, p. 12.) Pope et al. found that HLA class II genes expressing the RA-shared motif were present in 9 out of 11 patients genotyped for HLA-DRB1 and DQB1 alleles. (*Id.*) One of four immunodominant peptides is the 165-172 peptide sequence, which shares the first five amino acids (WASVRFSWA) with the last five amino acids (YLWEWASVR) of the 161-169 peptide sequence described by Pope et al. as a candidate rheumatoid epitope. (*Id.*) Additionally, the 96-104 peptide sequence, which Pope et al. describes as a potential binding region to the rheumatoid haphlotype, shares the first three amino acids (VLL) with the final 80-98 peptide sequence of HBsAg, which exhibits an a-helix conformation and identifies a T helper (CD4+) epitope. (*Id.*) Despite not completely overlapping with the rheumatoid epitope described by Pope et al., both the 165-172 and 80-98 peptide sequences share an anchor with the Major Histocompatibility Complex, Class II (MHC class II) binding

pocket. (*Id*.) Dr. Akbari notes the authors' conclusion that "polymorphic residues in the binding site of the MHC class II molecules in the affected patients appear capable of binding some peptide sequences from the recombinant vaccine." (*Id.* at 13.) Thus, the study suggests that the hepatitis B vaccine may trigger development of RA through peptide binding in individuals that are genetically susceptible due to their MHC class II profile. (*Id*.) He contends that this conclusion is supported by a study by Maillefert et al., which concluded that hepatitis B vaccination may trigger the onset of underlying inflammatory or autoimmune rheumatic diseases. (*Id.* (citing J.F. Maillefert et al., *Rheumatic Disorders Developed After Hepatitis B Vaccination*, 38 RHEUMATOLOGY 978 (1999) (Exs. 35, 64)); Ex. 49, p. 13 (citing Maillefert et al., *supra*, at Ex. 64).) A one-year follow-up study reported statistically significant increases in chronic arthritis following adult hepatitis B vaccination with an attributable risk of 5.1-9.0 per million vaccinations when compared to the control group. (Ex. 49, p. 13 (citing D.A. Geier & M.R. Geier, *A One Year Followup of Chronic Arthritis Following Rubella and Hepatitis B Vaccination Based Upon Analysis of the Vaccine Adverse Events Reporting System (VAERS) Database*, 20 CLINICAL & EXPERIMENTAL RHEUMATOLOGY 767 (2002) (Ex. 65)).)

In response to Dr. Mecoli's criticism of petitioner's experts' reliance on studies finding only a temporal association between vaccination and RA, Dr. Akbari explains that "[t]he infrequency of rare diseases makes it challenging to gather substantial data, and the potential associations with vaccination may require more specialized and targeted studies." (Ex. 14, p. 19.) Dr. Akbari emphasizes the importance of "approach[ing] the evaluation of rare diseases with a nuanced perspective" and provides a detailed explanation of why current study methods are unlikely to capture rare adverse effects. (*Id.* at 19-22.) On the issue of timing, Dr. Akbari disputes Dr. Bates's reliance on an animal model that included treatment with proteins and Complete Freund's Adjuvant and demonstrated a 7-10 day onset of RA. (Ex. 49, p. 8.) Dr. Akbari opines that animal models may not capture the genetic variability in humans. (*Id*.) Additionally, regulatory T cells, which are essential for the control of dysregulated immune responses, in mice are not comparable to humans. (*Id.* at 8-10.) Dr. Akbari notes that murine models have been found to exhibit a higher number of robust regulatory T cells, resulting in higher suppressive capacity to maintain peripheral immune tolerance, and murine regulatory T cells "display greater heterogeneity and plasticity in their subsets, allowing them to adapt and exert different regulatory functions in varied immune environments." (*Id.* at 9.) He cites additional studies showing how the flu vaccine leads to production of IL-1 as early as 30 minutes after vaccination (*Id.* at 2-3 (citing Nikolaos Chatziandreou et al., *Macrophage Death Following Influenza Vaccination Initiates the Inflammatory Response that Promotes Dendritic Cell Function in the Draining Lymph Node*, 18 CELL REPS. 2427 (2017) (Ex. 50); Crooke et al., *supra*, at Ex. 51; Weichun Tang et al., *Post-Vaccination Serum Cytokines Levels Correlate with Breakthrough Influenza Infections*, 13 SCI. REPS. 1 (2023) (Ex. 53))), as well as a study showing arm soreness and elevated temperature at the injection site that correlated with inflammasome-dependent cytokine IL-1β and production of other cytokines, such as TNF-α, within one day (*Id.* at 2 (citing Lisa M. Christian et al., *Proinflammatory Cytokine Responses Correspond with Subjective Side Effects After Influenza Virus Vaccination*, 33 VACCINE 3360 (2015) (Ex. 52))).

Dr. Akbari further emphasizes genetic susceptibility and environmental factors as crucial to the development of RA. (Ex. 14, pp. 15, 23.) He explains a central example of genetic susceptibility involves the association between certain MHC alleles and autoimmunity, such as HLA-DR1 or HLA DR4/HLA B27 in patients who developed RA or systemic lupus erythematosus following vaccination. (*Id.* at 15.[13]) In another example, Asakawa et al. described a patient who developed RA following flu vaccination. (*Id.* (citing Junichi Asakawa et al., *Reactive Arthritis After Influenza Vaccination: Report of a Case*, 15 MOD. RHEUMATOLOGY 283 (2005) (Ex. 37)).) This patient was found to have a negative rheumatoid factor, but human leukocyte antigen (HLA) typing analysis revealed positive results for HLA-B54, which Dr. Akbari opines is cross-reactive to HLA-B27. (*Id.*) Dr. Akbari further explains that "there are heterogeneous T-cell responses based on genetic differences in the genes that regulate the expression of antigen-presenting cells" and that "[t]his genetic difference can increase the potential for cross-reactivity from immunization in some individuals." (*Id.* at 16 (citing Christina M. Caporale et al., *Susceptibility to Guillain-Barré Syndrome Is Associated to Polymorphisms of CD1 Genes*, 177 J. NEUROIMMUNOLOGY 112 (2006) (Ex. 38)).) As for environmental factors, Dr. Akbari opines that nutrition, exercise, smoking, stress, and gut microbiota, as well as certain infections, such as mycoplasma pneumonia, cytomegalovirus, and flu, have been linked to RA. (*Id.*) Relevant here, Dr. Akbari notes that a meta-analysis by Sugiyama et al. provides only "marginal evidence" that smoking is a risk factor for RA in women. (*Id.* at 17 (citing D. Sugiyama et al., *Impact of Smoking as a Risk Factor for Developing Rheumatoid Arthritis: A Meta-Analysis of Observational Studies*, 69 ANNALS RHEUMATIC DISEASES 70 (2010) (Ex. 40)).) Specifically, the study found that female heavy smokers had a 1.3 times higher risk of developing RA compared to non-smokers. (*Id.* (discussing Sugiyama et al., *supra*, at Ex. 40).) However, these results were "significantly lower compared to men" (*Id.* (discussing Sugiyama et al., *supra*, at Ex. 40)), and other studies could not confirm a significant association between heavy smoking and RA in women, despite finding such an association in men (*Id.* (citing Eswar Krishnan et al., *Smoking-Gender Interaction and Risk for Rheumatoid Arthritis*, 5 ARTHRITIS RSCH. & THERAPY R158 (2003) (Ex. 41); Markku Heliövaara et al., *Smoking and Risk of Rheumatoid Arthritis*, 20 J. RHEUMATOLOGY 1830 (1993) (Ex. 42))). Furthermore, Dr. Akbari notes that studies finding an association between smoking and RA were limited to "heavy smoking," which is defined as 25 or more cigarettes per day, while petitioner reportedly only smoked about 10 cigarettes per day. (*Id.* at 18.)

In sum, Dr. Akbari explains that the age of the vaccinee, genetic changes of molecules that influence regulatory T cell generation or activation, the time and type of vaccination, and the magnitude of inflammation are all factors involved in the exacerbation of autoimmunity. (Ex. 14, pp. 6, 23 (citing Ren-Xi Wang et al., *Interleukin-35 Induces Regulatory B Cells that Suppress CNS Autoimmune Disease*, 20 NATURE

[13] Dr. Akbari included the following hyperlink in his report: https://pubmed.ncbi.nlm.nih.gov/9178394/. (Ex. 14, p. 15 n.3.) The link leads to: V. Ferrazzi et al., *Inflammatory Joint Disease After Immunizations: A Report of Two Cases*, 64 REVUE RHUMATISME ENG. ED. 227 (1997). However, the provided link includes only the article's abstract, and the full article has not been otherwise filed.

MED. 633 (2014) (Ex. 18); Christian Dejaco et al., *Imbalance of Regulatory T Cells in Human Autoimmune Diseases*, 117 IMMUNOLOGY 289 (2006) (Ex. 19)); *see also* Ex. 49, p. 6.) He emphasizes, however, that the subject vaccinations are the relevant environmental trigger in this case. (Ex. 14, pp. 17-18, 23.) Finally, Dr. Akbari opines that the timing between the subject vaccinations and onset of petitioner's RA "is consistent with the immune-mediated mechanism" underlying his causal theory. (*Id.* at 24.)

c. Respondent's Rheumatology Expert, Christopher A. Mecoli, M.D., M.H.S.[14]

Dr. Mecoli authored three expert reports on behalf of respondent. (Exs. A, C-D.) Dr. Mecoli disagrees that petitioner's hepatitis B vaccination more likely than not caused her RA. (Ex. A, p. 8; Ex. C, p. 2.) He notes that RA is a "relatively common autoimmune disease" that presents in approximately 1% of the population and disproportionately affects women. (Ex. A, p. 3.) RA is typically characterized by joint pain, swelling, autoantibody production, and destruction of cartilage and bone. (*Id*.) In some cases, patients may also develop systemic features, such as cardiovascular and pulmonary disease. (*Id*.) Although the pathogenesis of RA is unknown, it is generally believed that "a multifactorial, stepwise process occurs leading to a breakdown in immune tolerance." (*Id*.) Dr. Mecoli agrees with Dr. Gershwin's opinion that both genetic factors, such as germline and somatic mutations of genes, and environmental factors, such as smoking and alterations of the microbiome, can lead to a breakdown in immune tolerance. (*Id.* at 4; Ex. C, p. 1.) He further agrees that several factors likely play a role in the pathogenesis as "an accumulation of enough factors over time in the right context can break immune tolerance," eventually leading to development of clinical symptoms. (Ex. A, p. 4.) Moreover, Dr. Mecoli acknowledges that vaccines elicit an immune response, including cytokine, chemokine, and complement activation. (Ex. C, p. 1.)

However, Dr. Mecoli disputes Dr. Gershwin's claim that "the hepatitis B vaccine is implicated in the pathogenesis of rheumatoid arthritis generally, much less the petitioner's specific case of rheumatoid arthritis." (Ex. C, p. 1.) He explains that the

[14] Dr. Mecoli received his medical degree from Rutgers University in 2011, before going on to complete an internship and residency at the University of Pennsylvania in 2012 and 2014, respectively, as well as a fellowship in rheumatology at Johns Hopkins Hospital in 2017. (Ex. E, p. 1.) Also in 2017, Dr. Mecoli earned a master's degree in health sciences from Johns Hopkins Bloomberg School of Public Health, as well as an Ultrasound School of North American Rheumatologists (USSONAR) Certification. (*Id*.) He is board-certified in internal medicine and rheumatology, and he maintains an active medical license in Maryland. (*Id.* at 8.) He currently works as the Director of Research Operations at the Johns Hopkins Myositis Center, the Director of Myositis Precision Medicine Center Initiative, and as an assistant professor of medicine in the Division of Rheumatology at the Johns Hopkins University. (*Id.* at 1.) In his clinical capacity, Dr. Mecoli works as an attending physician of rheumatology at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center. (*Id*.) He regularly evaluates and treats "patients with inflammatory arthritis, as well as mimics of rheumatic disease, such as drug toxicity, paraneoplastic processes, and degenerative conditions." (Ex. A, p. 1.) He has authored, *inter alia*, 46 original research publications, 6 review articles, 2 book chapters, and 1 case report. (Ex. E, pp. 1-6.)

literature cited by Dr. Gershwin described a theoretical construct for how autoimmune disease may develop without specifically implicating the hepatitis B vaccine. (*Id*.) In that regard, Dr. Mecoli disputes Dr. Gershwin's causal theory as lacking a biological framework specific to the hepatitis B vaccine. (Ex. A, p. 5.) He notes that Dr. Gershwin has not presented any studies identifying the constituents of the hepatitis B virus or vaccine and demonstrating its ability to break immune tolerance. (*Id.*; Ex. C, p. 1.) Although Dr. Mecoli acknowledges that rheumatology experts have in the past expressed concern for a possible relationship between the hepatitis B vaccine and autoimmune conditions, such as RA, he emphasizes that the medical literature has found no association between the hepatitis B vaccine and RA. (Ex. A, pp. 5-6.) For example, he cites an editorial by Sibilia & Maillefert, which noted several case reports and case series observing a temporal relationship between hepatitis B vaccination and onset of RA, as well as epidemiologic studies in the form of large-scale hepatitis B vaccination programs that failed to find a statistically significant association. (*Id.* at 5 (citing J. Sibilia & J. F. Maillefert, *Vaccination and Rheumatoid Arthritis*, 61 ANNALS RHEUMATIC DISEASES 575 (2002) (Ex. A, Tab 2)).) In response to the conflicting data, the World Health Organization's Global Advisory Committee on Vaccine Safety investigated whether subjects with genetic susceptibility to RA (two subgroups of HLA DRB1*04) are at increased risk of RA following hepatitis B vaccination. (*Id.* at 6 (citing World Health Org., *Global Advisory Committee on Vaccine Safety, 12-13 December 2007*, 83 WKLY. EPIDEMIOLOGICAL REC. 37 (2008) (Ex. A, Tab 3)).) The study found "no statistically significant evidence of increased risk in the genetic subgroup examined." (*Id.* (quoting World Health Org., *supra*, at Ex. A, Tab 3).) Follow up studies confirmed a lack of association. (*Id.* (citing Camilla Bengtsson et al., *Common Vaccinations Among Adults Do Not Increase the Risk of Developing Rheumatoid Arthritis: Results from the Swedish EIRA Study*, 69 ANNALS RHEUMATIC DISEASES 1831 (2010) (Ex. A, Tab 4); Ray et al., *supra*, at Ex. A, Tab 5; *see also* Ex. 33).) For example, a large case-control study of 1,998 incident cases of RA and 2,252 randomly selected controls matched for age and sex found "no signal of increased risk of RA in patients who received any hepatitis vaccination." (*Id.* (citing Bengtsson et al., *supra*, at Ex. A, Tab 4).) The authors further investigated a subgroup of subjects thought to be at higher risk for developing RA due to genetic factors (HLA-DRB1-01, HLA-DRB1-04, HLA-DRB1-10 alleles) or environmental factors (smoking) and again found no association between hepatitis vaccination and RA. (*Id.* at 7 (citing Bengtsson et al., *supra*, at Ex. A, Tab 4).)

Dr. Mecoli further disputes Dr. Akbari's causal opinion. (Ex. D.) First, he asserts that Dr. Akbari's implication of both the hepatitis B and flu vaccines as causal in "an 'either/or' argument" underscores our lack of knowledge regarding how either vaccine may influence development of RA. (*Id.* at 1.) Second, although he agreed that vaccines can lead to inflammasomes and Th17 activation, Dr. Mecoli disagrees that the data supports a role for inflammasomes and Th17 activation in the pathogenesis of RA, specifically. (*Id*.) Third, Dr. Mecoli acknowledges that flu vaccination has been temporally associated with development of RA (*Id.* at 1-2); however, he asserts that "evidence of causality has not been demonstrated in my opinion" (*Id.* at 1). He notes that the only study cited by Dr. Akbari that takes into account the base incidence rate of RA in the general population concluded that there is no relationship between either the

hepatitis B vaccine or the flu vaccine and development of RA. (*Id.* at 2 (citing Ray et al., *supra*, at Ex. 33).)

Dr. Mecoli also observes that Dr. Gershwin's causal theory is predicated on a temporal association between petitioner's vaccination and onset of her RA. (Ex. A, p. 5.) He asserts that a temporal association alone is insufficient to support causation and that, in any event, such temporal association is likely coincidental. (*Id.* at 5, 7.) Dr. Mecoli notes Dr. Gershwin's opinion that petitioner was "at-risk of RA given her history and likely long-standing [rheumatoid factor]/CCP positivity" (*Id.* at 7), though he clarifies that petitioner's experts' suggestion that she had a genetic predisposition to RA is speculative (Ex. D, p. 2). He ultimately states that "[w]hether the petitioner would have developed rheumatoid arthritis given her potential genetic susceptibility and smoking history is unknown but it is a reasonable scenario in my opinion." (Ex. A, p. 7; *see also* Ex. D, p. 2 (emphasizing petitioner's history of smoking).) Dr. Mecoli further asserts that petitioner's respiratory infection approximately three weeks prior to onset is likely "another potential contributor to the development of the petitioner's RA." (Ex. A, p. 7; *see also* Ex. D, p. 2.) He notes that respiratory infections have been posited as one of the contributing factors in the pathogenesis of RA. (Ex. A, p. 7; Ex. D, p. 2.)

d. Respondent's Immunology Expert, John T. Bates, Ph.D.[15]

Dr. Bates authored two expert reports on behalf of respondent. (Exs. F, H.) Dr. Bates disputes Dr. Akbari's theory as not supported by peer-reviewed scientific literature or the course of petitioner's condition as documented in her medical records. (Ex. F, p. 4.) He first disputes Dr. Akbari's opinion that flu vaccination results in activation of the inflammasome and a pathological Th17-biased CD4+ T cell response. (*Id.*; Ex. H, p. 1.) Dr. Bates contends that none of the cited references demonstrate activation of the inflammasome by the seasonal inactivated flu vaccine. (Ex. F, p. 4.) He emphasizes that the papers by Crooke et al. and Wan et al. focus on flu infection, rather than vaccination; that the papers by Yang et al. and Hartenian & Broz focus on Kaposi's Sarcoma Herpes Virus and its proteins, which are not comparable to the flu virus or vaccine; that the paper by Bermejo-Martin et al. investigates immune response to infection with "severe pandemic influenza," which is not comparable to the immune response to seasonal flu vaccination; and that the paper by Lin et al. discusses a "DNA vaccine expressing protective antigen and IL-23," which is not comparable to the

[15] Dr. Bates received his Ph.D. in microbiology from the University of Alabama at Birmingham in 2005, before going on to complete a post-doctoral fellowship in the Department of Microbiology and Immunology at Wake Forest University School of Medicine in 2010, followed by a second post-doctoral fellowship in the Vanderbilt Vaccine Center at Vanderbilt University School of Medicine in 2014. (Ex. G, p. 1.) He is broadly trained in immunology with special experience in the study of innate response, as well as both branches of the adaptive response, to vaccination. (Ex. F, p. 1.) He currently works as an associate professor for the Department of Medicine and the Department of Cell and Molecular Biology at the University of Mississippi Medical Center (UMMC). (Ex. G, p. 2.) Additionally, Dr. Bates presently serves as the Scientific Director of the Human Immunology and Inflammation Biomarker Core Laboratory at UMMC, a member of the UMMC Center for Immunology and Microbial Research, and a member of the Mississippi Clinical Research and Trials Center. (*Id.*) He has authored 33 publications and participated in 15 posters and oral presentations. (*Id.* at 3-5, 10-12.)

seasonal flu vaccine. (*Id.* at 4-5 (citing Crooke et al., *supra*, at Ex. 22; Wan et al., *supra*, at Ex. 23; Yang et al., *supra*, at Ex. 24; Hartenian & Broz, *supra*, at Ex. 25; Bermejo-Martin et al., *supra*, at Ex. 29; Lin et al., *supra*, at Ex. 30).) Regarding the paper by Chatziandreou et al., Dr. Bates observes that the figure relied upon by Dr. Akbari reports IL-1α levels, not IL-1β levels. (Ex. H, pp. 1-2 (citing Chatziandreou et al., *supra*, at Ex. 50, p. 7).) He explains that IL-1α and IL-1β have some overlapping biological effects, but different pathways control the expression and release of these cytokines. (*Id.* at 2.) Notably, expression of IL-1α does not require activation of the inflammasome. (*Id.*) Regarding the paper by Christian et al., Dr. Bates explains that the serum cytokine levels are very low; that the authors omitted a p-value for IL-1β, suggesting that differences between the IL-1β readings were not significant; and that an association between IL-1β levels and soreness existed prior to vaccination and thus unrelated to vaccination. (*Id.* (citing Christian et al., *supra*, at Ex. 52).)

Dr. Bates also disputes Dr. Akbari's opinion that hepatitis B vaccination results in activation of the inflammasome. (Ex. F, pp. 6-7.) Dr. Bates asserts that he could not locate any reports in the medical literature to support Dr. Akbari's opinion that hepatitis B surface antigen activates innate pathogen sensing pathway or pathogen recognition receptors. (*Id.* at 7.) Instead, the literature suggests that hepatitis B surface antigen has immunosuppressive properties and inhibits innate immune activation. (*Id.* (citing Mohammad Enamul Hoque Kayesh et al., *Toll-Like Receptor Response to Hepatitis B Virus Infection and Potential of TLR Agonists as Immunomodulators for Treating Chronic Hepatitis B: An Overview*, 22 INT'L J. MOLECULAR SCIS. 1 (2021) (Ex. F, Tab 4)).) Additionally, Dr. Bates opines that "it is widely accepted that the adjuvant activity of alum is mediated via the inflammasome." (*Id.* at 6.) To support this assertion, Dr. Bates cites a study, finding that the response to vaccination with alum in animals with genetically inactivated inflammasome pathways is significantly reduced compared to the response in normal animals. (*Id.* at 6-7 (citing Hanfen Li et al., *Cutting Edge: Inflammasome Activation by Alum and Alum's Adjuvant Effect Are Mediated by NLRP3*, 181 J. IMMUNOLOGY 17 (2008) (Ex. F, Tab 3)).)

Dr. Bates further disputes Dr. Akbari's claim that vaccination has been documented to cause rheumatic complications as not supported by the cited medical literature. (Ex. F, pp. 7-8.) He notes that the paper by Symmons & Chakravarty describes two patients who received either the flu or hepatitis B vaccine, but neither patient met the criteria for RA, and the authors did not make any causal conclusions, despite noting case reports and case series that have suggested vaccine causation. (*Id.* at 7 (citing D.P.M. Symmons & K. Chakravarty, *supra*, at Ex. 31).) Basra et al. presents a single case report and discusses genetic susceptibility to RA in Mexican Americans, which is not relevant here. (*Id.* (citing Basra et al., *supra*, at Ex. 32).) The epidemiologic study by Ray et al. found that the possible association between flu vaccination and RA discovered in the cohort study was not borne out in the larger case-control study. (*Id.* (citing Ray et al., *supra*, at Ex. 33).) The authors also found that the relative risk of RA within 90, 180, and 365 days of hepatitis B vaccination was not significant after adjusting for sex, race, and number of utilization visits. (*Id.* (citing Ray et al., *supra*, at Ex. 33).) Dr. Bates submits that Pope et al. is not relevant as we do not

know petitioner's HLA type. (*Id.* at 7-8 (citing Pope et al., *supra*, at Ex. 34).) Finally, the study by Maillefert et al. stops short of establishing a causal relationship between hepatitis B vaccination and rheumatic manifestations. (*Id.* at 8 (citing Maillefert et al., *supra*, at Ex. 35); Ex. H, p. 4.) Dr. Bates explains that the study's methods, which included a questionnaire of rheumatology patients, resulted in selection bias as no unaffected or healthy participants were surveyed. (Ex. F, p. 8 (discussing Maillefert et al., *supra*, at Ex. 35).) Moreover, the criteria for inclusion in this small study of just 22 participants was onset of "rheumatic complaints" during the two months after hepatitis B vaccination with no previously diagnosed rheumatic disease and "no other explanation for the complaints." (Ex. H, p. 4 (quoting Maillefert et al., *supra*, at Ex. 64).) Similarly, Geier & Geier is based on data drawn from the VAERS database, which is insufficient to prove a causal connection.[16] (*Id.* at 5 (citing Geier & Geier, *supra*, at Ex. 65).)

Regarding Dr. Akbari's opinion on genetic susceptibility, Dr. Bates acknowledges that humans are genetically heterogenous and can respond differently to the same stimuli. (Ex. H, p. 3.) However, he disputes Dr. Akbari's reliance on the papers by Fourati et al. and Hagan et al. (*Id.* at 2-3.) Fourati et al. shows that individuals "can have different pre-vaccination gene transcription profiles that are predictive of their response to vaccination based on antibody titers." (*Id.* at 2 (citing Fourati et al., *supra*, at Ex. 55).) However, this paper focuses on pre-vaccination endotypes or transcription signals and does not involve adverse events following vaccination. (*Id.* at 2-3.) Dr. Bates further points to the study's finding that "pre-vaccination inflammatory endotypes explained 12.5% of the variance in gene expression observed before and after vaccination," which he explains indicates that the effect is modest, and "[o]n average, participants from the inflam.hi endotype, which had the highest pre-vaccination levels of pro-inflammatory pathways, showed *reduced* vaccine-induced expression of pro-inflammatory pathways." (*Id.* at 3 (emphasis added) (quoting Fourati et al., *supra*, at Ex. 55).) Dr. Bates does not dispute the Hagan et al. study's ultimate finding that different vaccines elicit different transcriptional profiles, or "clusters," across vaccinated individuals; however, he submits that Dr. Akbari misinterprets the study by referring to "clusters" as groups of patients that respond differently to vaccination. (*Id.* (citing Hagan et al., *supra*, at Ex. 56).)

Regarding timing, Dr. Bates opines that petitioner's medical records support an onset of 3.5 days post-vaccination. (Ex. F, p. 8.) Dr. Bates disagrees this timeframe is consistent with a vaccine-mediated injury. (*Id.*) He explains that Drs. Gershwin and Akbari base their theory on an innate immune response; however, in animal models involving injection of very reactogenic adjuvant (Complete Freund's Adjuvant), arthritis did not develop until 10 days after vaccination. (*Id.* at 9 (citing Carl M. Pearson et al.,

[16] I also note respondent's concern regarding petitioner's reliance on the article by Geier & Geier because the authors "have been largely discredited as experts in the Vaccine Program." (ECF No. 67, p. 8.) It is true that these authors have been heavily criticized in prior Program decisions. *See, e.g.*, *America v. Sec'y of Health & Human Servs.*, No. 17-542, 2022 WL 278151, at *8 n.16 (Fed. Cl. Spec. Mstr. Jan. 4, 2022); *Hooker v. Sec'y of Health & Human Servs.*, No. 02-472V, 2017 WL 3033940, at *15-16 (Fed. Cl. Spec. Mstr. Apr. 11, 2017); *Doe/03 v. Sec'y of Health & Human Servs*., 2007 WL 2350645, at *3 & nn.8-9 (Fed. Cl. Spec. Mstr. July 31, 2007). However, I do not need to reach any conclusions regarding the credibility of these authors to resolve the instant case.

Studies of Arthritis and Other Lesions Induced in Rats by Injection of Mycobacterial Adjuvant, 113 J. EXPERIMENTAL MED. 485 (1961) (Ex. F, Tab 5)); Ex. H, pp. 3-4.) Although he acknowledges that animal models have limitations in their ability to mirror human disease, he opines that these studies are still useful for understanding possible timelines for human adverse events. (Ex. H, pp. 3-4.) He also points out that, in general, the antigen doses and adjuvants used in animal models are "much higher" than those used in human vaccines, suggesting that one would expect disease onset to be quicker in animals receiving higher doses. (*Id.* at 4.) Dr. Bates also points to Geier & Geier, which observed VAERS reports of chronic arthritis following hepatitis B vaccination with a mean onset of 16 days. (*Id.* at 5 (citing Geier & Geier, *supra*, at Ex. 65).) This time interval is closer to the 7-10 days seen in animal models than to the 3-day onset reported by petitioner. (*Id*.) He further notes petitioner's reliance on a study by Ray et al., which looked at time intervals of 90, 180, and 365 days after vaccination, and opines that this study suggests that "RA following vaccination likely occurs weeks to months following vaccination rather than on the order of days." (Ex. F, p. 8 (discussing Ray et al., *supra*, at Ex. 33).)

That said, Dr. Bates agrees that "the innate immune response to vaccination is well underway within 24 hours of vaccination." (Ex. F, p. 9.) He suggests, however, that it is more likely that petitioner's concurrent respiratory infection, which would have resulted in an innate immune response in excess of the level of innate activation stimulated by flu or hepatitis B vaccination, triggered her RA. (*Id*.) Dr. Bates cites a study by Ichinohe et al., which found that respiratory infection with flu virus results in activation of NLR inflammasomes in the lung. (*Id.* at 5 (citing Takeshi Ichinohe et al., *Inflammasome Recognition of Influenza Virus Is Essential for Adaptive Immune Responses*, 206 J. EXPERIMENTAL MED. 79 (2009) (Ex. F, Tab 1)).) However, Dr. Bates criticizes Dr. Akbari's treatment of immunization and infection as "equivalent biological events." (*Id*.) He notes that Ichinohe et al. observed that only stimulation with live virus results in significant production of IL-1β, while stimulation with heat- and UF-inactivated virus resulted in IL-1β in similar levels to controls. (*Id.* (citing Ichinohe et al., *supra*, at Ex. F, Tab 1).) A subsequent study by Ichinohe et al. expanded on this research, finding that activation of inflammasome requires proper localization of the ion channel; however, the "ion channel that is present in a preparation of inactivated virus or seasonal influenza vaccine would be unable to find its way into the cell and correctly insert itself into the membrane of the Golgi apparatus." (*Id.* (citing Takeshi Ichinohe et al., *Influenza Virus Activates Inflammasomes Via Its Intracellular M2 Ion Channel*, 11 NATURE IMMUNOLOGY 404 (2010) (Ex. F, Tab 2)).) Dr. Bates argues that these two studies demonstrate Dr. Akbari's misplaced reliance on studies concerning the flu virus to support his inflammasome theory as it relates to the subject vaccines. (*Id.* at 4-6.) He further emphasizes Dr. Gershwin's opinion that respiratory infections are a risk factor for RA. (*Id.* at 9-10.) An additional factor unrelated to vaccination that could have caused petitioner's RA is her history of smoking. (*Id.* at 10.)

V. Analysis

As discussed above, petitioner's burden of proof in a cause-in-fact claim is to meet the three-part *Althen* test, which includes (1) a general theory of causation implicating the vaccine as a cause of the alleged condition, (2) a logical sequence of cause and effect implicating the vaccination as a cause of petitioner's own condition, and (3) appropriate timing of onset based on the theory of causation. 418 F.3d at 1278. In this case, the parties present issues with respect to all three *Althen* prongs. However, for the reasons discussed below, petitioner's inability to meet her burden under *Althen* prong one is dispositive. Therefore, the remaining *Althen* prongs are addressed only briefly.

a. Petitioner has not met her burden of proof under *Althen* prong one

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the subject vaccine can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (quoting *Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004)). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *See Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory." *Boatmon*, 941 F.3d at 1359 (quoting *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)). "While it does not require medical or scientific certainty, it must still be 'sound and reliable.'"[17] *Id.* at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

[17] In her motion, petitioner argues that her burden of proof under *Althen* prong one is only to present a "biologically plausible" theory of causation rather than demonstrating a legally persuasive theory based on a preponderance of the evidence. (ECF No. 48, pp. 10-12 (discussing, for example, *Doe 93 v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 553, 566-67 (2011)).) Petitioner asserts that the *Althen* court set forth a "plausible medical theory element" and she contends that, although subsequent Federal Circuit precedents lack clarity, this *Althen* formulation is better interpreted as having been affirmed rather than overturned by subsequent court panels. (*Id*. at 10, 12 (citing *Kottenstette v. Sec'y of Health & Human Servs.*, 861 F. App'x 433, 440-41 (Fed. Cir. 2021)).) However, following petitioner's filing, this question has been more definitively resolved by the Federal Circuit. In *Cerrone v. Secretary of Health & Human Services*, the Federal Circuit explicitly rejected the argument that a petitioner need only demonstrate a "biologically plausible" theory. 146 F.4th 1113, 1120-21 (Fed. Cir. 2025) (explaining that petitioner's argument regarding a biologically plausible theory "understates the burden he bears under the first factor in the *Althen* formulation"). Instead, a petitioner must meet a preponderant burden of proof under the first *Althen* prong demonstrating the vaccine at issue can cause the injury alleged via "sound and reliable medical or scientific explanation," even as it is not necessary to reach scientific certainty. *Id*. at 1121.

i. Capizzano *is not controlling*

As a threshold matter, petitioner cites *Capizzano v. Secretary of Health & Human Services*, 440 F.3d 1317 (Fed. Cir. 2006), as proof that "[t]he Hepatitis B vaccine has been accepted in the Vaccine Program as the cause of RA." (ECF No. 48, p. 19.) She emphasizes that the *Capizzano* court relied on the Maillefert study, also filed in this case and discussed below, as well as the findings of the Institute of Medicine regarding rechallenge cases, as providing "such strong proof of causality that it is unnecessary to determine the mechanism." (*Id.* at 19-21 (quoting *Capizzano v. Secretary of Health & Human Services*, Nos. 00-759V, 01-221V, 99-609V, 99-591V, 99-628V, 2003 WL 22425000, at *4 (Fed. Cl. Spec. Mstr. Aug. 5, 2003).) Thus, petitioner appears to imply that any analysis of whether the hepatitis B vaccine can cause RA should stop at citation to the Federal Circuit's opinion affirming the *Capizzano* special master's causal findings as they relate to *Althen* prong one.

Importantly, however, neither the *Capizzano* special master's nor the Federal Circuit's causal analyses are binding. Indeed, the Federal Circuit has explicitly observed that "[a] special master's acceptance of a theory in one case does not require him or her to accept the theory in subsequent cases involving similar facts or the same vaccine." *Rickett v. Sec'y of Health & Human Servs.*, 468 F. App'x 952, 959 (Fed. Cir. 2011). And while 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), the Federal Circuit has also stressed that "[c]ausation in fact under the Vaccine Act is . . . based on the circumstances of the particular case," *Boatmon*, 941 F.3d at 1358-59 (quoting *Knudsen*, 35 F.3d at 548). Accordingly, Federal Circuit precedents do not automatically control the outcome of subsequent cases even when they involve the same injury. *See, e.g.*, *Sanchez v. Sec'y of Health & Human Servs.*, 809 F. App'x 843, 852 (Fed. Cir. 2020) (citing back to a prior Federal Circuit holding in *Paluck v. Secretary of Health & Human Services*, and noting with regard to the two Leigh's Syndrome cases that "while there are substantial parallels between this case and *Paluck*, the differences between the two cases are such that the outcome of this case is not dictated by *Paluck*").

Thus, other special masters have not been persuaded by attempts to rely on *Capizzano* as providing a presumption of causation in cases involving the hepatitis B vaccine and RA. *See Bean-Sasser v. Sec'y of Health & Human Servs.*, No. 13-326V, 2016 WL 1649355, at *8-9 (Fed. Cl. Spec. Mstr. Apr. 5, 2016), *mot. for rev. denied*, 127 Fed. Cl. 161 (2016); *Jones v. Sec'y of Health & Human Servs.*, No. 19-3V, 2020 WL 2954960, at *3 (Fed. Cl. Spec. Mstr. Apr. 29, 2020). The special master in *Bean-Sasser* explained that the chief special master in *Capizzano* determined that the hepatitis B vaccine can cause RA "in the context of a 'rechallenge'" and, given the limited scope of the issues on appeal, "the Federal Circuit's recitation of fact-finding by the special master does not transform those facts into a statement of law that binds special masters in subsequent cases." 2016 WL 1649355, at *9.

Moreover, I and other special masters have repeatedly held that there is insufficient evidence to implicate vaccination as a cause or trigger of RA. *Casazza v. Sec'y of Health & Human Servs*., No. 17-947V, 2023 WL 6214984, at *10 (Fed. Cl. Spec. Mstr. Aug. 30, 2023) (explaining that "there is no dispute that RA is an autoimmune condition of uncertain cause that generally involves a combination of genetic and environmental factors or stimuli . . . [but] [v]ery little on this record apart from Dr. Gershwin's say-so associates any vaccine with RA whereas much more purports to refute Dr. Gershwin's opinion"); *Powell v. Sec'y of Health & Human Servs.*, No. 20-1726V, 2025 WL 3443590, at *33 (Fed. Cl. Spec. Mstr. Oct. 8, 2025) (describing prior cases finding that petitioner failed to preponderantly show that the flu vaccine can cause RA); *Aultman v. Sec'y of Health & Human Servs.*, No. 21-1802V, 2025 WL 2401983, at *22 (Fed. Cl. Spec. Mstr. July 11, 2025) (citing prior cases denying claims alleging vaccine-caused RA); *Maxwell v. Sec'y of Health & Human Servs.*, No. 17-1367V, 2025 WL 1291642, at *30 (Fed. Cl. Spec. Mstr. Mar. 26, 2025) (same); *see also Clark v. Sec'y of Health & Human Servs.*, No. 17-1553V, 2023 WL 4897284, at *32 (Fed. Cl. Spec. Mstr. June 16, 2023); *Moran v. Sec'y of Health & Human Servs.*, No. 16-538V, 2021 WL 4853544, at *30 (Fed. Cl. Spec. Mstr. Oct. 4, 2021); *Hock v. Sec'y of Health & Human Servs.*, No. 17-168V, 2020 WL 6392770, at *23-27 (Fed. Cl. Spec. Mstr. Sept. 30, 2020); *Tullio v. Sec'y of Health & Human Servs.*, No. 15-51V, 2019 WL 7580149, at *22 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), *mot. for rev. denied*, 149 Fed. Cl. 448 (2020); *Wilson v. Sec'y of Health & Human Servs.*, No. 17-1264V, 2023 WL 9053671, at *17 (Fed. Cl. Spec. Mstr. Dec. 7, 2023); *Seivwright v. Sec'y of Health & Human Servs.*, No. 19-1398V, 2023 WL 3197267, at *2 (Fed. Cl. Spec. Mstr. May 2, 2023). *But see Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 673 (2011) (utilizing a biological plausibility standard, which has since been rejected, to determine entitlement to compensation for flu vaccine-caused RA); *H.J. v. Sec'y of Health & Human Servs.*, No. 11-301V, 2015 WL 6848357, at *12 (Fed. Cl. Spec. Mstr. Nov. 6, 2015) (finding that the Tdap vaccine can cause RA in a patient with overlap syndrome and preclinical disease).

Ultimately, while I am mindful of the analyses in *Capizzano*, as in *Bean-Sasser*, the evidence presented here differs from the evidence that was before the chief special master in *Capizzano*, namely, petitioner's experts' causal theories do not involve rechallenge. Moreover, as discussed below, additional medical literature, including articles post-dating *Capizzano*, further undermines petitioner's showing as to *Althen* prong one.

ii. The mechanisms advanced by petitioner are not persuasive

Both Dr. Gershwin and Dr. Akbari devote significant attention to discussing the fact that RA is an autoimmune condition, to explaining that is multifactorial in cause, and to discussing the immune responses involved. These broader points are mostly not disputed. (*Compare* Ex. 7, pp. 2, 6, *and* Ex. 14, pp. 5, 15, 23, *with* Ex. A, pp. 3-4.) However, the fact that a condition is autoimmune does not automatically lead to the conclusion that vaccination(s) can be implicated. The parties disagree on whether there

is preponderant evidence to support that the subject vaccines can cause RA. (ECF No. 48, p. 34; ECF No. 56, p. 28.) To that point, petitioner submits that her experts have presented preponderant evidence of several possible mechanisms by which the subject vaccines can be implicated as a cause RA. (ECF No. 48, pp. 21, 30-31.)

"Of course, petitioners are never required to establish [a] mechanism—but they often attempt to do so, and therefore it is reasonable to evaluate their success in the effort." *Howard v. Sec'y of Health & Human Servs*., No. 16-1592V, 2022 WL 4869354, at *24 (Fed Cl. Spec. Mstr. Aug. 31, 2022), *mot. for rev. denied sub nom.*, *Howard v. United States*, No. 16-1592V, 2023 WL 4117370 (Fed. Cl. May 18, 2023), *aff'd per curiam*, No. 2023-1816, 2024 WL 2873301 (Fed. Cir. June 7, 2024). That is, although petitioner's *Althen* prong one showing need not reach scientific certainty and, moreover, she is not obligated to provide "detailed medical and scientific exposition on the biological mechanisms," her theory must ultimately be preponderantly supported, which may be accomplished via sound and reliable medical or scientific explanation. *Cerrone v. Sec'y of Health & Human Servs.*, 146 F.4th 1113, 1121 (Fed. Cir. 2025) (quoting *Knudsen*, 35 F.3d at 549).) "[T]o say that proof in the form of epidemiological studies or well-established medical experience is not mandatory does not mean that the special masters in Vaccine Act cases are precluded from inquiring into the reliability of testimony from expert witnesses." *Moberly*, 592 F.3d at 1325.

Accordingly, each of the mechanisms advanced by petitioner are examined in turn. For the reasons discussed below, none are persuasively presented, whether considered individually or collectively.

a. Challenge-rechallenge

Following on from her discussion of *Capizzano*, petitioner argues that the Maillefert paper demonstrates via challenge-rechallenge that the hepatitis B vaccine can cause RA. (ECF No. 48, pp. 20-21 (discussing Maillefert et al., *supra*, at Exs. 35, 64).) While petitioner is correct that rechallenge cases *can* provide a basis for establishing causation (*Id*. (citing *James-Cornelius v. Sec'y of Health & Human Servs*., 984 F.3d 1374, 1381 (Fed. Cir. 2021)), the Maillefert authors do not present the case reports at issue as "strong proof of causality" in the manner petitioner suggests (*Id*. (quoting *Capizzano*, 2003 WL 22425000, at *4)).

The Maillefert authors did observe that "[f]or a majority of patients, the temporal association was suggestive" and "[t]he manifestations worsened in most of the patients who were given a further injection." (Maillefert et al., *supra*, at Ex. 35, p. 5.) And, notably, they considered these arguments as favoring a causal relationship. (*Id.*) However, they also observed that, as an observational retrospective study, their work was not designed to respond to the question of whether the temporal relationship at issue was causal or coincidental. (*Id.*) The study utilized a questionnaire to identify six women who experienced RA within two months of hepatitis B vaccination, with four of those six women experiencing a relapse after a second injection. (*Id.* at 2.) Studies relying on similar methodology have been afforded less weight in prior cases. *See, e.g.*,

Meyers v. Sec'y of Health & Human Servs., No. 19-272V, 2025 WL 2754664, at *23 (Fed. Cl. Spec. Mstr. Aug. 22, 2025); *DeVaughn v. Sec'y of Health & Human Servs.*, No. 22-832V, 2025 WL 758128, at *20 (Fed. Cl. Spec. Mstr. Feb. 10, 2025); *Johnson v. Sec'y of Health & Human Servs.*, No. 14-254, 2018 WL 2051760, at *24 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) (criticizing a study's use of a population of subjects that voluntarily sought treatment as "too self-selected to draw conclusions from correlations observed with respect to that population"); *Evanson v. Sec'y of Health & Human Servs.*, No. 90-775V, 1991 WL 179085, at *4 (Fed. Cl. Spec. Mstr. Aug. 28, 1991) (criticizing a study that necessarily relied on self-reporting). Ultimately, the authors' conclusion was only tentatively stated. They suggested that "hepatitis vaccine might be followed by various rheumatic conditions and might trigger the onset of underlying inflammatory or autoimmune rheumatic diseases. However, a causal relationship between hepatitis B vaccination and the observed rheumatic manifestations cannot be easily established." (Maillefert et al., *supra*, at Ex. 35, p. 5.)

Although challenge-rechallenge is a valid concept, based on my review, the Maillefert paper does not preponderantly establish that challenge-rechallenge occurred among the six case subjects or otherwise preponderantly establish a causal relationship between the hepatitis B vaccine and RA. Notably, although Dr. Akbari cited the Maillefert paper and its ultimate conclusion, he did not incorporate challenge-rechallenge into his own opinion (Ex. 14, p. 13), and Dr. Gershwin did not discuss the paper at all (Exs. 7, 13).

b. Molecular mimicry

Petitioner additionally invokes molecular mimicry (albeit without using the term) to explain how the hepatitis B vaccine can cause RA. (ECF No. 48, p. 22.) Specifically, petitioner quotes Dr. Akbari's explanation that a study by Pope et al. showed peptide sequences from immunodominant peptides that shared five amino acids with a candidate rheumatoid epitope.[18] (*Id*. at 22-23; *see also* Ex. 14, pp. 12-13 (citing Pope et al., *supra*, at Ex. 34).)

Although molecular mimicry "is a generally accepted scientific principle, mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 28, 2019)). Prior cases have explained that when assessing theories based on molecular mimicry in light of petitioner's preponderant burden of proof, "[t]he line must be drawn somewhere between speculation and certainty." *Brayboy v. Sec'y of Health & Human Servs.*, No.

[18] The theory of molecular mimicry posits that autoimmune disease arises when a foreign antigen (e.g., vaccine antigen) resembles self-antigens, leading to the production of antibodies that, in an attempt to protect against the foreign antigens, mistakenly attack the self-antigens. *See Tullio*, 2019 WL 7580149, at *12; *Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *4 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd per curiam*, 540 F. App'x 999 (Fed. Cir. 2013).

15-183V, 2021 WL 4453146, at *19 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). In particular, "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio*, 2019 WL 7580149, at *15; *see also Caredio ex rel. D.C. v. Sec'y of Health & Human Servs.*, No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021) ("[D]emonstration of homology alone is not enough to establish a preponderant causation theory." (emphasis omitted) (citing *Schultz v. Sec'y of Health & Human Servs.*, No. 16-539V, 2020 WL 1039161, at *22 n.24 (Fed. Cl. Spec. Mstr. Jan. 24, 2020))), *mot. for rev. denied*, No. 17-79V, 2021 WL 6058835 (Fed. Cl. Dec. 3, 2021).

Ultimately, the Pope study does not provide strong evidence supporting an invocation of molecular mimicry and Dr. Akbari's reports otherwise lack any explication of the concept or any other evidence to support its applicability. Although Dr. Akbari is correct that the study identified *potentially* relevant amino acid sequence matches, the thrust of the study was to examine genetic susceptibility to RA. (Pope et al., *supra*, at Ex. 34, p. 6 (explaining that "[o]ur studies suggest that genetic factors linked to MHC class II molecules may represent a risk factor for post-vaccine arthritis but there are undoubtedly other determining factors . . .").) Thus, on respondent's behalf, Dr. Bates noted that the Pope study "is not generalizable to the population as a whole or specifically to the petitioner because we do not know the petitioner's HLA type." (Ex. F, p. 8.) But in any event, although the study authors discuss "[p]redictions of binding" based on the identified sequences, nothing in the study actually examines whether such binding occurs or substantiates that the degree of sequence overlap identified would be sufficient to be disease-causing. (Pope et al., *supra*, at Ex. 34, p. 6.) That is, the study is limited to identifying *potential* homologies.[19] Thus, while the study certainly appears to have potential as a starting point to assert a theory based on molecular mimicry, it is not sufficient on its own. Specifically, the study authors explained:

> In summary, our report describes the appearance of arthritis, usually persistent, and often fulfilling criteria for RA, after vaccination with recombinant hepatitis B vaccine in previously healthy individuals. This uncommonly reported outcome should alert others to look for this association. Further studies are required to confirm whether this association is other than coincidental.

(*Id*.)

And, indeed, Dr. Gershwin opined on petitioner's behalf that it is "neither clinically nor scientifically possible" to retrospectively identify the peptides involved. (Ex. 13, p.

[19] In Tables 3 and 4, Pope et al. provide a summary of the potential binding of the vaccine peptides to the MHC class II polymorphic residues encoded by the DRβ1 alleles in each of the study participants. (Pope et al., *supra*, at Ex. 34, pp. 5-6, tbls. 3-4.) The authors identified two sequences of 9 amino acids as candidates for the rheumatoid epitope from the 226 amino acid long peptide sequence contained in the hepatitis B vaccine. (*Id.* at 6, tbl. 4.) Of those sequences, only four peptides (P1, P4, P6, P9) were identified as "MHC II binding pockets of importance." (*Id*.) Dr. Akbari does not provide any opinion regarding whether the degree of homology identified is sufficient to trigger cross-reaction leading to disease.

1.) Dr. Akbari's additional citation to Maillefert et al. as further support for the Pope study's conclusions does not remedy these deficiencies. After describing the existing literature, including their own findings, the Maillefert authors explain that "data suggest[s] that there is apparently no difference between cases of RA following hepatitis B vaccination and other RA." (Maillefert et al., *supra*, at Ex. 35, p. 4.) As explained above, the authors acknowledge that "it is difficult to know whether there is a coincidental or a causal relationship between immunization and the observed rheumatic manifestations," and they specifically disclaim that their observational retrospective study was performed to address the issue of causation. (*Id.* at 5.)

c. Inflammasomes

Dr. Akbari also opines that "many recent articles showed that inflammasome directly plays an important role in the induction of RA." (Ex. 14, p. 11.) He, in turn, asserts that both the flu vaccine and hepatitis B vaccine can activate inflammasomes. (*Id*. at 6-10.) Citing Yin et al., Dr. Akbari opines that the NLRP3 inflammasome, which he in turn associates with IL-1β, "might" be implicated in the pathogenesis of RA. (Ex. 14, p. 7 (citing Yin et al., *supra*, at Ex. 21).) Following on from that point, he cites Crooke et al. for the proposition that "inflammasome and subsequent production of IL-1 and related genes get sufficiently triggered by the flu vaccination, in the absence of adjuvants." (*Id*. at 8 (citing Crooke et al., *supra*, at Ex. 22).) He then cites several other papers for the proposition that "viruses such as influenza are capable of inducing inflammasome." (*Id*. at 8-9 (citing Wan et al., *supra*, at Ex. 23; Yang et al., *supra*, at Ex. 24; Hartenian & Broz, *supra*, at Ex. 25).)[20] By contrast, Dr. Akbari proposes via *ipse dixit* a multi-step process whereby the hepatitis B vaccine can be similarly implicated, but via the alum adjuvant within the vaccine. (*Id*. at 9-10.)

Dr. Mecoli observes, however, that while vaccinations may activate inflammasomes, it remains speculative to suggest that this in turn renders vaccinations a cause of RA. (Ex. D, p. 1 (stating that "I agree vaccines can lead to inflammasome and Th17 activation; however, to state this response to vaccination is causally related to the pathogenesis of RA is not supported by data").) To Dr. Mecoli's point, it is notable that, even with all of the literature petitioner has filed discussing inflammasomes and all the literature petitioner has filed with respect to RA (*see, e.g.*, ECF No. 48-1, *passim*), nothing apart from Dr. Akbari's say-so marries any discussion of post-vaccination inflammasome activity with discussion of the pathogenesis of RA. Moreover, the Yin paper cited by Dr. Akbari is the only piece of literature petitioner filed directly addressing the possible role of inflammasome NLRP3 in the pathogenesis of RA; however, the paper's conclusions are only tentatively stated. Specifically, the authors explain that "[r]ecent studies *suggest* that NLRP3 inflammasome, a regulator of inflammation, *might* play an important role in the development of RA." (Yin et al., *supra*, at Ex. 21, p. 1 (emphasis added).) Indeed, Dr. Akabari himself repeated this exact phrasing in his report. (Ex. 14, p. 7.) And, notably, petitioner's rheumatology expert, Dr. Gershwin, did

[20] Notably, whereas Dr. Akbari initially discussed the NLRP3 inflammasome in the pathogenesis of RA, the Yang and Hartenian papers addressed NLRP1. (Yang et al., *supra*, at Ex. 24; Hartenian & Broz, *supra*, at Ex. 25.)

not include inflammasomes in his extensive discussion of the pathophysiology of RA. (Exs. 7, 13.) Moreover, Dr. Gershwin stresses that one must distinguish the immune cells or factors that explain the initiation of disease from those that are responsible for perpetuating the disease. (Ex. 7, pp. 5-6.) Even if crediting that inflammasomes play some part in the RA disease process, Dr. Akbari's citation to the Yin paper does not, without more, establish that inflammasomes are responsible for initiation, rather than mediation, of RA.

Dr. Bates further stresses that "[n]one of [Dr. Akbari's] references demonstrate activation of the inflammasome by the seasonal inactivated influenza vaccine." (Ex. F, p. 4.) He further charges that "Dr. Akbari treats immunization and infection as equivalent biological events." (*Id*. at 5.) While Dr. Akbari has cited several studies regarding live viruses, Dr. Bates cites two studies by Ichinohe et al., which he asserts to have specifically shown that inactivated viruses do not generate IL-1β comparable to infection. (*Id*. (citing Ichinohe et al., *supra*, at Ex. F, Tab 1; Ichinohe et al., *supra*, at Ex. F, Tab 2).) Of the papers cited by Dr. Akbari, only Crooke et al. involved vaccination. (*Id.* at 4-5; *see also* Crooke et al., *supra*, at Ex. 22.) However, it was not a direct study of vaccine effects. (Ex. F, p. 4 (discussing Crooke et al., *supra*, at Ex. 22.) Instead, "[c]ells from vaccinated individuals were infected with influenza virus. Infection with of cells with virus is not biologically equivalent to stimulation with inactivated virus or equivalent to in vivo vaccination." (*Id*. (discussing Crooke et al., *supra*, at Ex. 22).) In response to this criticism, Dr. Akbari cited Chatziandreou et al. to further support the proposition that the flu vaccine produces IL-1. (Ex. 49, pp .1-2 (citing Chatziandreou et al., *supra*, at Ex. 50).) However, Dr. Bates pointed out that, whereas Dr. Akbari might reasonably use IL-1β as a surrogate for inflammasome activation, Chatziandreou et al. addressed IL-1α, rather than IL-1β. (Ex. H, p. 2 (discussing Chatziandreou et al., *supra*, at Ex. 50).) Although there is some overlap, IL-1α and IL-1β operate by different pathways and IL-1α is not dependent on activation of the inflammasome. (*Id*.) Thus, Chatziandreou et al. does not buttress Dr. Akbari's opinion.

Regarding the hepatitis B vaccine, Dr. Bates explains that Dr. Akbari's theory proposes that hepatitis B surface antigen would act as "signal 1," which is required for priming and activation of inflammasomes. (Ex. F, p. 7; *see also* Ex. 14, p. 10.) However, although this has been a very active area of immunology research, Dr. Bates indicates that no literature supports Dr. Akbari's proposition. (Ex. F, p. 7.) Instead, the literature that is available suggests that hepatitis B surface antigen has immunosuppressive properties. (*Id*. (citing Kayesh et al., *supra*, at Ex. F, Tab 4).) According to Dr. Bates, based on current understanding, inflammasomes require both a "signal 1" and "signal 2" for activation, but Dr. Akbari has neither shown what "signal 1" would be within his proposed theory, nor demonstrated that hepatitis B surface antigen would behave in that manner. (*Id*.) Based on my review of his responsive report, I do not see where Dr. Akbari attempted to directly address this shortcoming. (Ex. 49.) Instead, Dr. Akbari's further discussion of inflammasome activation focused overwhelmingly on the flu, rather than hepatitis B, vaccine. (*Id*.)

d. Regulatory and Effector T cells

Dr. Akbari further opines that disruption in the balance of regulatory T cells and effector T cells can lead to autoimmunity. (Ex. 14, pp. 10-11, 13-14; Ex. 49, pp. 8-11.) He identifies Th17, an effector T cell that secretes IL-17, as involved in the pathogenesis of various rheumatic diseases. (Ex. 14, pp. 5, 11 (citing Zambrano-Zaragoza et al., *supra*, at Ex. 15).) Specifically, a shift in the balance towards effector T cells (such as Th17 cells) causes a decrease in regulatory T cell levels and effector T cells hyper-activation leading to autoimmune disorders such as RA. (*Id.* at 11.) He explains that studies have shown that patients with RA have increased levels of Th17 cells in their peripheral blood and joints, and that patients who have been infected with or vaccinated against flu have elevated levels of IL-17 and Th17. (*Id.* at 5, 11 (citing Egan et al., *supra*, at Ex. 16; Bermejo-Martin et al., *supra*, at Ex. 29; Lin et al., *supra*, at Ex. 30).)

However, Dr. Akbari has not substantiated that vaccination would throw off this homeostasis. Indeed, even as Dr. Akbari opines that vaccines elevate effector T cells, he also observes that "[i]nduction of [effector T] cells can cause protection or pathology." (Ex. 14, p. 14; *see also* Lin et al., *supra*, at Ex. 30, p. 8 (noting the "fine balance between protection and pathological manifestations of Th17 responses" as an important area of inquiry for future vaccine development).) Therefore, he acknowledges that "the number . . . and the capability of [effector T cells] (often by secreting cytokines) need to be considered in relation to the number and function of [regulatory T cells] (Treg/Teff ratio)." (Ex. 14, p. 14.) Yet, he also acknowledges that "[v]accines are known to stimulate the [regulatory T cells] and [effector T cells] in normal individuals after influenza immunization." (*Id*.) Dr. Akbari merely speculates that the outcome would be different among those genetically susceptible. (*Id*.) And, although Dr. Akbari otherwise discussed genetic susceptibility factors (*e.g.*, *id.* at 15-16), nothing in that separate discussion substantiates this particular aspect of Dr. Akbari's opinion. Indeed, Dr. Akbari's discussion of genetics would seem, if anything, to complicate his reliance on the Treg/Teff ratio.[21] Dr. Akbari cited a single study with respect to the specific proposition that the influenza vaccine would affect T cell homeostasis after flu vaccination. (I. Herrero-Fernández et al., *Effect of Homeostatic T-Cell Proliferation in*

[21] For example, discussing major histocompatibility complexes Dr. Akbari indicates that:

> The greatest problem is the limited numbers of subjects in the genome association studies. These complexes are expressed on certain types of immune cells, called antigen presenting cells, to the B cells and T cells to induce the production of antibodies. For example, studies show that response to the vaccines is not dominated by universal CD4+ T cell epitopes. This means that there are heterogeneous T-cell responses based on genetic differences in the genes that regulate the expression of antigen-presenting cells. This genetic difference can increase the potential for cross-reactivity from immunization in some individuals. Accordingly, this also can account for some of the reason that reactions to vaccines are so rare.

(Ex. 14, p. 16 (internal citation omitted).) Moreover, he observes that while some genetic differences may be associated with disease susceptibly, others may instead be associated with disease severity. (*Id*. at 15.)

the Vaccine Responsiveness Against Influenza in Elderly People, 16 IMMUNITY & AGING 1 (2019) (Ex. 36).) However, that study did not examine adverse effects. The study's conclusion was only that among subjects with a pre-existing inflammatory state inclusive of higher levels of regulatory T cells at baseline there was reduced responsiveness to the vaccine. (*Id*. at 8.) Even setting aside vaccination specifically, the Bermejo-Martin authors otherwise specifically noted that further investigation is needed to determine whether Th17 plays a beneficial or detrimental role in the immune response to the A/H1N1 pandemic influenza virus. (Bermejo-Martin et al., *supra*, at Ex. 29, p. 8.)

e. Cytokines

I also note in the interest of completeness that Dr. Akbari discussed RA as being mediated in part by pro-inflammatory cytokines, paying particular attention to IL-17, TNF-α, and IL-1β. (Ex. 14, pp. 5, 10-11.) However, although he did specifically assert that the flu vaccine produced elevations in IL-17 (*Id*. at 11), Dr. Akbari's discussion of cytokines appears to have been preface to, and intertwined with, his discussion of inflammasomes and T cells, which are otherwise addressed above. (*Id.* at 9-11; Ex. 49, pp. 4-5, 7.) Based on my review, Dr. Akbari has not articulated any standalone theory that would posit a direct relationship between post-vaccination cytokines and RA.

In any event, petitioner would not meet her burden by simply pointing to the undisputed fact that vaccines induce some immune response without providing additional proof linking the otherwise-intended effect of the subject vaccine to the injury at issue. *See Kaltenmark v. Sec'y of Health & Human Servs.*, No. 17-1362V, 2023 WL 8870299, at *28 (Fed. Cl. Spec. Mstr. Nov. 27, 2023) (the undersigned observing that "[e]ven where there is some reason to suspect a condition may be cytokine mediated, this does not automatically lead to the conclusion that vaccines can cause the injury merely because vaccines produce some cytokine elevations"); *Gaskin v. Sec'y of Health & Human Servs.*, No. 21-835V, 2025 WL 786306, at *10 (Fed. Cl. Spec. Mstr. Feb. 11, 2025) (explaining that "mere invocation of a vaccine's intended immune response is not in and of itself sufficient to carry petitioner's burden under *Althen* prong one" and that "[t]here must be some additional evidence linking the vaccine's immune response to the pathology of petitioner's actual condition"); *see also Dean ex rel. I.D. v. Sec'y of Health & Human Servs.*, No. 13-808V, 2017 WL 2926605, at *16-18 (Fed. Cl. Spec. Mstr. June 9, 2017) (explaining in the context of alleged encephalopathy that, even though "[m]any of the general principles (as evidenced by Petitioner's expert reports plus the filed medical or scientific literature) that underlie this theory are not disputed," "[t]he most immediately apparent weakness in this case's causation theory is the heavy lifting it assigns to the post-vaccination cytokine production process as the cause of almost all of the pathologic effects of the vaccines at issue").

f. Additional mechanisms cited by Dr. Gershwin

Although petitioner's motion focuses primarily on Dr. Akbari's opinion, she also notes that Dr. Gershwin "summed up several possible mechanisms by which either or

both the influenza vaccine and the Hepatitis B vaccine can be a substantial factor in the onset of RA." (ECF No. 48, pp. 30-31.) Specifically, "[h]e stated RA can be triggered by 'mechanisms of bystander activation, production of pro-inflammatory cytokines, alterations of nucleic acid sensors, and of course, innate immunity and finally disruption of T and B regulatory pathways.'" (*Id*. at 31 (quoting Ex. 7, p. 6).)

Without explaining how these mechanisms can work together, Dr. Gershwin opines that more than one of the proposed pathways is likely involved. (Ex. 7, p. 6.) However, he does not provide any specific support for any of these mechanisms relative to the pathogenesis of RA, and his cursory overview does not provide sufficient detail to explain how the hepatitis B (or the flu) vaccine can cause RA via any of the proposed mechanisms. He contends that "only through the use of newer high throughput technologies will final recognition of disease-specific pathways be defined" (*Id.*), and even accounting for the fact that petitioner is not required to demonstrate scientific certainty, *Boatmon*, 941 F.3d at 1359, Dr. Gershwin has not provided preponderant evidence to support a sound and reliable medical theory in this case.

iii. The record evidence does not favor an association between the vaccines at issue and RA

While petitioner need not present epidemiology to meet her burden of proof, *Capizzano*, 440 F.3d at 1325, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory," *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018). Thus, "where such evidence is submitted, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury." *Andreu*, 569 F.3d at 1379. Petitioner cites Ray et al., an epidemiologic study assessing the risk of developing RA following vaccination against tetanus, flu, and hepatitis B. (Ray et al., *supra*, at Ex. 33.) However, the authors concluded: "In this large retrospective study we found no statistically significant association between exposure to hepatitis B vaccine and onset of RA. A possible association between RA and influenza vaccination in the cohort study was not borne out in the larger case-control analysis." (*Id.* at 1.)

Apart from Ray et al., petitioner's experts cite primarily to papers purportedly showing an association between flu and hepatitis B vaccination and RA via case reports and case series. For example, Symmons & Chakravarty explain that "[t]here is a substantial body of evidence, much of it anecdotal, that immunisation may precipitate arthritis in some individuals." (Symmons & Chakravarty, *supra*, at Ex. 31, p. 1.) Basra et al. describe a single case report of a woman who experienced joint pain in her hands, wrists, and knees within a week of receiving a seasonal flu vaccine, which resolved within a few days, then later developed more extensive symptoms following a subsequent swine flu vaccination, and was ultimately diagnosed with RA. (Basra et al., *supra*, at Ex. 32, p. 1.) Petitioner also cites a case report describing a 79-year-old man

who developed reactive arthritis following a flu vaccination.[22] (Asakawa et al., *supra*, at Ex. 37.)

While case reports are not entirely without evidentiary value, they are not strong evidence without more. *E.g.*, *Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-0039V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) (noting that "single case reports of Disease X occurring after Factor Y . . . do not offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance"), *aff'd*, 125 Fed. Cl. 251 (2014); *see also Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (indicating that case reports "do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value. . . [but] the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight" (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011))).

On respondent's behalf, Dr. Mecoli argues that, given the frequency of flu and hepatitis B vaccination and the fact that RA is "a relatively common rheumatic disease," numerous instances of vaccination temporally associated with onset of RA is to be "expected." (Ex. D, pp. 1-2.) Although he acknowledges case reports and case series suggesting a temporal association between vaccination and RA (Ex. A, pp. 5-6 (citing Sibilia & Maillefert, *supra*, at Ex. A, Tab 2)), Dr. Mecoli opines that subsequent studies, including a large case-control study, found no association between either flu or hepatitis B vaccination and RA (*Id.* at 6-7 (citing Bengtsson et al., *supra*, at Ex. A, Tab 4)). He emphasizes that the only reference cited by petitioner that takes into account the background rate of RA is a study by Ray et al. (Ex. D, p. 2 (citing Ray et al., *supra*, at Ex. 33).) Notably, Dr. Akbari limits his reliance on Ray et al. as proof of "a possible temporal association" between flu and hepatitis B vaccination and onset of RA. (Ex. 14, p. 12 (discussing Ray et al., *supra*, at Ex. 33).)

iv. Drs. Gershwin and Akbari are not persuasive on the whole

Finally, I stress that, although I have delineated specific aspects of Drs. Gershwin's and Akbari's opinion for discussion as above, I have considered that the concepts raised by petitioner's experts could collectively represent a whole greater than the sum of its parts. I conclude that they do not. Drs. Gershwin and Akbari included extensive discussion of a variety of immune concepts in a broader discussion of autoimmunity. For example, Dr. Akbari filed nearly 50 articles to support his causal opinions. And, although I have reviewed all of the filings, I do not find it necessary to describe in detail each piece of medical literature to explain why I am not persuaded by their presentations. Without more, broad reliance on autoimmune processes is inadequate. *Apuzzo v. Sec'y of Health & Human Servs.*, No. 17-1915V, 2024 WL 4534200, at *23 (Fed. Cl. Spec. Mstr. Sep. 20, 2024) (explaining that "it is not enough,

[22] Reactive arthritis is not comparable to RA. (Maillefert et al., *supra*, at Ex. 35, p. 4 (describing rheumatic conditions as a distinct group from transient post-vaccinal arthritis); *Casazza*, 2023 WL 6214984, at *17 (noting that "while the clinical signs of RA and reactive arthritis may overlap, Dr. Gershwin was very clear in describing two distinct causal mechanisms for reactive arthritis and RA respectively").)

as Dr. Gupta implies, to simply rely on the fact that Sjögren's syndrome, CIDP, and small fiber neuropathy are all autoimmune conditions. Simply, it is too vague to preponderantly support a theory of causation" (internal citations omitted)), *mot. for rev. denied*, 176 Fed. Cl. 206 (2025).

There are various pathways to autoimmunity, and many autoimmune conditions have little to no suspicion of vaccine causation. *E.g.*, *Kelly v. Sec'y of Health & Human Servs.*, No. 16-1548V, 2023 WL 3274159, at *9 (Fed. Cl. Spec. Mstr. May 5, 2023) (explaining that "[t]here is little debate that myasthenia gravis is an autoimmune neuromuscular disorder and there is little debate that molecular mimicry is, in general, a viable theory of autoimmunity that can in at least some contexts implicate vaccination. Importantly, however, these predicates are not enough to meet petitioner's burden of proof"); *Casazza*, 2023 WL 6214984, at *10 (explaining "there is no dispute that RA is an autoimmune condition of uncertain cause" and that "[v]ery little on this record apart from Dr. Gershwin's say-so associates any vaccine with RA whereas much more purports to refute Dr. Gershwin's opinion"). In this case, Drs. Gershwin and Akbari, despite discussing extensively the immunology underlying autoimmunity, and despite also discussing the uncontroversial fact that vaccines do elicit an intended immune response, have not preponderantly supported the notion that these discussions can be combined to demonstrate that either of the vaccines at issue in this case would have any meaningful effect on the pathophysiology leading to RA.

Accordingly, I find that petitioner has not met her burden under *Althen* prong one of showing by preponderant evidence that the flu or hepatitis B vaccine can cause RA.

b. *Althen* prongs two and three in brief

Because I have concluded that petitioner has not demonstrated that the flu or hepatitis B vaccines likely can cause RA, it is not necessary to address in detail whether the vaccine did so in this particular case. Given the outcome regarding *Althen* prong one, by definition it likely did not. *Trollinger v. Sec'y of Health & Human Servs.*, 167 Fed. Cl. 127, 142 (2023) (affirming the Chief Special Master's dismissal based on a dispositive finding that petitioner had not satisfied *Althen* prong one). However,

> When applying *Althen*, the special master must consider the degree to which each factor is satisfied. And then, after weighing the degree to which the petitioner has proved each factor and considering any remaining evidence bearing on causation, the special master must determine whether the petitioner has proved that it is more likely than not that the vaccine caused [her] injury.

Cerrone, 146 F.4th at 1122 (citing *Andreu*, 569 F.3d at 1382).

Therefore, I briefly note with respect to *Althen* prongs two and three that the evidence relevant to petitioner's own history is not so robust as to otherwise cast doubt on the analysis under *Althen* prong one. *See, e.g.*, *Patton v. Sec'y of Health & Human*

Servs., 157 Fed. Cl. 159, 169 (2021) (finding treating physician opinions relevant to assessing the reliability of the expert's theory of general causation). In particular, even if one were to assume *arguendo* that the vaccinations petitioner received can cause RA, her medical history is not one that calls out for such an explanation.

Whereas under the first *Althen* prong, petitioner must present a general medical theory explaining that the vaccine in question "can" cause the type of injury in question, *Pafford*, 451 F.3d at 1355-56, under the second and third prongs petitioner must also present evidence that the vaccine "did" cause petitioner's own injury. *Id*. The third prong asks whether the timing of injury in this specific case aligns with what would be expected under the general theory presented under *Althen* prong one. *Id.* at 1358. The second *Althen* prong requires preponderant proof of a logical sequence of cause and effect, which is usually supported by facts derived from petitioner's medical records.[23] *Althen*, 418 F.3d 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. However, while the opinions of treating physicians are often favored, *Capizzano*, 440 F.3d at 1326, a petitioner may support a cause-in-fact claim through presentation of either medical records or an expert medical opinion. *See* § 300aa-13(a).

The Federal Circuit has cautioned that the second *Althen* prong "is not without meaning," but has also indicated that satisfaction of *Althen* prongs one and three is probative with respect to *Althen* prong two. *Capizzano*, 440 F.3d at 1326-27. Nonetheless, temporal association alone is not enough to satisfy petitioner's burden of proof. *See*, *e.g.*, *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting [the] vaccine and injury"), *aff'd per curiam sub nom.*, *Veryzer v. United States*, 475 F. App'x 765 (Fed. Cir. 2012); *A.Y. v. Sec'y of Health & Human Servs.*, 152 Fed. Cl. 588, 595 (2021); *Forrest v. Sec'y of Health & Human Servs.*, No. 10-032V, 2017 WL 4053241, at *18 (Fed. Cl. Spec. Mstr. Aug. 10, 2017); *Cozart v. Sec'y of Health & Human Servs.*, No. 00-590V, 2015 WL 6746616, at *18 (Fed. Cl. Spec. Mstr. Oct. 15, 2015), *mot. for rev. denied*, 126 Fed. Cl. 488 (2016); *Crosby v. Sec'y of Health & Human Servs.*, No. 08-799V, 2012 WL 13036266, at *37 (Fed. Cl. Spec. Mstr. June 20, 2012).

In this case, although petitioner pointed out that her treating rheumatologist repeatedly documented that she had provided a history of symptoms beginning two weeks post-vaccination, she did not identify any instance in which he, or any other

[23] Medical records are generally viewed as trustworthy evidence. *Cucuras*, 993 F.2d at 1528. These records are generally contemporaneous to the medical events and "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium." *Id.* However, medical records and/or statements of a treating physician's views do not *per se* bind the special master. § 300aa-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, 745 n.67 (2009) (reasoning that "nothing . . . mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

treating physician, actually opined that her condition was vaccine caused. (ECF No. 48, p. 32 (citing Ex. 1, p. 39).) A treating physician's mere reference to a temporal relationship between vaccination and symptoms is not equivalent to drawing a causal connection. *Moberly*, 592 F.3d at 1323-24; *Isaac v. Sec'y of Health and Human Servs*., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012) (explaining that "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation"), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd per curiam*, 540 F. App'x 999 (Fed. Cir. 2013). Thus, based on my review of the medical records, there is no treating physician support for petitioner's claim.

By contrast, petitioner's treating physicians did repeatedly opine that smoking is a risk factor for RA and advised her to quit smoking (*e.g.*, Ex. 1, p. 55; Ex. 5, p. 8; Ex. 6, pp. 11, 16), a point with which respondent's experts concur (Ex. A, p. 4; Ex. D, p. 2; Ex. F, p. 10). Additionally, there is no meaningful dispute among the parties' experts that petitioner suffered an upper respiratory infection shortly before onset of her RA (Ex. 7, p. 6; Ex. A, p. 7; Ex. F, p. 10) and, further, no dispute that upper respiratory infections can cause RA to manifest (Ex. 7, p. 1; Ex. 14, pp. 17-18; Ex. A, p. 7; Ex. F, p. 10).[24]

The parties disagree as to the timing of onset. (*Compare* ECF No. 48, p. 33 (placing onset of RA within two-weeks post-vaccination), *with* ECF No. 56, pp. 24-25 (placing onset of RA at three or four days post-vaccination).)[25] But in any event, given that petitioner was vaccinated in the midst of experiencing her upper respiratory infection (*compare* Ex. 2, pp. 4, 7 (May 10 date of vaccination), *with* Ex. 1, p. 3 (May 13 report of three-week history of cold-like symptoms and worsening symptoms within the

[24] In her motion reply, petitioner takes issue with the fact that respondent has not presented epidemiologic evidence that upper respiratory infections are a cause of RA even as respondent is critical of petitioner for not presenting epidemiology to support her claim. (ECF No. 61, pp. 1-3.) However, this is of no moment, both because I have not held petitioner to any requirement to produce epidemiology and, regardless of what evidence respondent has filed, petitioner's own experts agree that upper respiratory infections can cause RA to manifest. (Ex. 7, p. 1; Ex. 14, p. 17.)

[25] Petitioner averred that she experienced onset of her symptoms "within a few days" of her vaccinations (Ex. 4, ¶ 3); however, she anchored her recollection to her first treatment encounter at urgent care, which she incorrectly recalled as having occurred on May 20, 2016 (*Id*.). In fact, that encounter occurred a month later, on June 20, 2016. (Ex. 2, p. 9.) At that encounter, petitioner clearly reported that her symptoms had been ongoing for three days and she associated the onset with a new job at a linen company, rather than her vaccination. (*Id*.) That record, which indicates petitioner may be seeking workers' compensation, documented that she had been in this new job for only one week and does not clearly state she had left that job. (*Id*. at 9-10.) When she presented to a primary care provider three days later, on June 23, 2016, it was initially remarked that her symptoms started "the morning of the 14th," which could be roughly consistent with the history she provided at urgent care if one assumes "the 14th" refers to the current month, but then confusingly indicates that she started her new job on May 13. (Ex. 1, p. 8.) However, petitioner also reported having had three jobs within the prior month (*Id*. at 10), making it difficult to pin-point this history. The next day, she reported to another provider that her symptoms began while she was employed at the linen company but also indicated that she had most recently been working as a dishwasher. (*Id*. at 14.) However, this same record indicates she had been experiencing symptoms for about a week. (*Id*.) Although it is impossible to confidently pin-point the timing of onset on this record, I am not persuaded that petitioner more likely than not was experiencing symptoms consistent with RA prior to about mid-June of 2016.

past few days), any proposed temporal relationship that would potentially favor a causal inference relative to petitioner's vaccines would likewise support a causal inference relative to her upper respiratory infection.

On petitioner's behalf, Dr. Akbari asserts that studies have found either no association or only "marginal evidence" that smoking is a risk factor for RA in women and that studies finding an association were limited to "heavy" smokers unlike petitioner. (Ex. 14, pp. 17-18 (citing Sugiyama et al., *supra*, at Ex. 40; Krishnan et al., *supra*, at Ex. 41; Heliövaara et al., *supra*, at Ex. 42).) However, even setting that risk factor aside, he clearly agrees that infection can trigger RA. (*Id.* (stating that "many studies clearly show that the induction of autoimmunity and RA in humans often requires an environmental trigger, such as infection or immunization").) Moreover, after emphasizing that RA is multifactorial, petitioner's other expert, Dr. Gershwin, suggested that petitioner's history of smoking, as well as her concurrent respiratory infection, at least played a role in the onset of her RA. (Ex. 7, p. 6.)

Petitioner is not obligated to rule out other causes of her condition or to demonstrate that vaccination was the sole cause of her condition, but the presence of other possible sources of injury can still be relevant to the determination of whether petitioner has met her prima facie burden of proof.[26] *Winkler*, 88 F.4th at 962-63. The notion that a perceived vaccine injury ultimately represents mere coincidence can sometimes seem unsatisfying. However, this is not such a case. The Federal Circuit has explained that a petitioner may fail to meet her burden of proof under *Althen* prong two where "the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant evidence." *Capizzano*, 440 F.3d at 1327. Here, given the nature of RA and its multi-step pathogenesis, petitioner's presumed genetic predisposition to RA (Ex. 7, p. 6; Ex. A, p. 7), her history of smoking (Ex. 1, pp. 3, 26, 55), and the upper respiratory infection she suffered shortly before onset of symptoms (*Id.* at 3-5), the medical history at issue is not one that reasonably requires any further explanation as to why her symptoms manifested when they did. Moreover, the lack of any meaningful treating physician suspicion for the alleged causal relationship to vaccination further underscores this point. Therefore, even if petitioner had met her burden of proof under *Althen* prong one, and even if further assuming the timing was potentially appropriate under *Althen* prong three, her experts would still not be persuasive in asserting with respect to *Althen* prong two that her vaccinations were an additional but for cause or substantial contributing factor in the development of her RA.

[26] Petitioner has not alleged in her briefing that the concomitant factors, *i.e.*, upper respiratory infection, history of smoking, *and vaccination*, caused her to suffer RA. Instead, petitioner specifically disputes respondent's attempts to implicate her upper respiratory infection or history of smoking as causal factors in this case. (ECF No. 48, pp. 32-33; ECF No. 61, pp. 2-3.)

VI. Conclusion

Although petitioner has my sympathy for the pain and discomfort she has endured, for all the reasons discussed above, I find that she has not met her burden of proof. Therefore, pursuant to § 300aa-12(d)(3)(A) and Vaccine Rule 10, this decision concludes that petitioner is not entitled to an award of compensation. Absent a timely motion for review, the Clerk is directed to enter judgment dismissing this case for insufficient proof in accordance with Vaccine Rule 11(a).

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master