In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 16-538V
Filed: October 4, 2021

JOSEPH MORAN, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	TO BE PUBLISHED Special Master Katherine E. Oler Ruling on the Record; Entitlement; Rheumatoid Arthritis; Influenza Vaccine.

Andrew D. Downing, Van Cott & Talamante, PLLC, Phoenix, AZ, for Petitioner
Althea W. Davis, U.S. Department of Justice, Washington, DC, for Respondent

DECISION ON ENTITLEMENT[1]

On May 2, 2016, Joseph Moran ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program[2] alleging that he suffered rheumatoid arthritis ("RA") as a result of the influenza ("flu") vaccination he received on October 17, 2013. Pet., ECF No. 1 at 1. For the reasons set forth below, I find that Petitioner has not preponderantly demonstrated the flu vaccine can cause RA or that it did so in this case.

[1] Because this Decision contains a reasoned explanation for the action in this case, I intend to post this Decision on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2012)). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the Decision in its present form will be available. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) ("Vaccine Act" or "the Act"). Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

I. Procedural History

Petitioner filed a statement of completion on May 26, 2016. ECF No. 9. On July 25, 2016, Respondent filed a Rule 4(c) Report recommending against compensation. ECF No. 11.

Petitioner filed an expert report authored by Dr. Thomas Zizic on October 27, 2016. Ex. 18, ECF No. 16, and supporting medical literature on December 5, 2016, ECF Nos. 19-21. On March 20, 2017, Respondent filed an expert report by Dr. Mehrdad Matloubian. Ex. A, ECF No. 26, and supporting medical literature on May 17, 2017. ECF Nos. 27-30. Petitioner then filed Dr. Zizic's rebuttal expert report on July 3, 2017. Ex. 49, ECF No. 31. On July 25, 2018, Respondent responded by filing Dr. Matloubian's second expert report. Ex. C, ECF No. 43.

On September 14, 2018, Petitioner filed a status report indicating his preference for a ruling on the record. ECF No. 45. On November 28, 2018, Petitioner filed his brief (ECF No. 47) and Respondent filed his response on April 2, 2019 (ECF No. 53). Petitioner filed a reply on April 9, 2019. ECF No. 54.

On May 23, 2019, I requested supplemental expert reports from each party responding to additional outstanding questions. ECF No. 56. Petitioner filed Dr. Zizic's report on July 1, 2019, Ex. 53, ECF No. 58, and Respondent filed Dr. Matloubian's report on July 22, 2019. Ex. D, ECF No. 59.

On August 7, 2019, I asked the parties to file a joint status report indicating that all evidence had been submitted and that no additional records needed to be filed. Non-PDF Scheduling Order of 8/7/2019. On August 27, 2019, the parties confirmed that the record is complete. ECF No. 60.

I held a status conference on February 10, 2020 where I informed the parties that I had more questions regarding *Althen* prong one that I did not believe could be answered by additional filings. Scheduling Order dated Feb. 10, 2020. ECF No. 61. I told the parties that I wanted to have an entitlement hearing so that I could hear the testimony of the experts and ask questions as necessary. *Id.*

I conducted an entitlement hearing via WebEx on August 18, 2020 and on October 26, 2020. The parties filed a joint status report on December 17, 2020 indicating that the record was complete. ECF No. 79. This matter is now ripe for a decision.

II. Medical History

Petitioner was born on May 1, 1958. Ex. 3 at 2. Petitioner received a flu vaccination on October 17, 2013. Ex. 2.

On December 4, 2013, Petitioner visited Tristan Guevara, DO at Silver Pine Medical Group. Ex. 7 at 16. The "History of Present Illness" ("HPI") section of the medical records from this visit states that Petitioner "present[ed] with cold symptoms[…]nasal congestion[,] and postnasal drainage…" *Id.* Petitioner stated that "[o]nset was sudden 2 month(s) ago." *Id*. His

symptoms included swollen lymph nodes, fatigue, and weakness. *Id*. The "Problem List/Past Medical" listed "[j]oint [p]roblems, "[j]oint aches," and "[b]ackache." *Id*. Petitioner was noted to be a "[f]ormer smoker" who "[q]uit [in] 1996." *Id*. He was diagnosed with acute sinusitis and prescribed amoxicillin, Flonase and Claritin-D. *Id*. at 17.

Petitioner returned to Silver Pine Medical Group on December 26, 2013. Ex. 7 at 14. He reported "cold symptoms," "nasal congestion," and "runny nose." *Id*. The "Problem List/Past Medical" again listed "[j]oint [p]roblems, "[j]oint aches," and "[b]ackache." *Id*. The nasal mucosa examination was described as "[b]oggy, [c]ongested and [p]ale" and the nasal septum was noted to be "deviated to left." *Id*. at 15. The assessment was acute sinusitis and noted that he had "failed amoxicillin." *Id*. He was prescribed Cefdinir and referred for his deviated septum. *Id*.

On January 16, 2014, Petitioner visited Shores Podiatry Associates. Ex. 6 at 1. The "[s]ubjective" portion of this records reads:

> Patient presents to office complaining of painful bilateral plantar foot. Patient reports increased activity leading to the onset of pain. Patient states he was having pain in the heel of his feet and when he was [at] a hockey game he was walking on the ball of his feet. This caused pain in the ball and ankle of his feet. The heel is feeling fine now. He is pointing to the right 4/5 [intermetatarsal] and left dorsal midfoot…

Ex. 6 at 1. The assessment included "neuroma, arthritis, tinea, [and] onychomycosis." *Id*. Petitioner received a dexamethasone phosphate and marcaine injection in his right foot. *Id*.

On February 11, 2014, Petitioner saw ENT Dr. Robert Fishman, who determined that "a lot of his symptoms [were] due to the dryness in the air and his allergies." Ex. 8 at 6. Dr. Fishman found no evidence of persistent sinusitis. *Id*.

On March 5, 2014, Petitioner returned to Dr. Guevara at Silver Pine Medical. Ex. 7 at 10. The HPI states "[t]he patient feels well with no complaints, has good energy level and is sleeping well." *Id*. The "Problem List/Past Medical" again listed "[j]oint [p]roblems, "[j]oint aches," and "[b]ackache." *Id*. The assessment included Plantar Fasciitis. *Id*. at 12.

Petitioner returned to the podiatrist on March 10, 2014. Ex. 6 at 3. The "[s]ubjective" section of this record states that "[p]atient presents with multiple complaints. Patient [complains of] pain in both feet & ankles. Patient has noted this problem for several months. Patient notes recurrent pain & swelling in the 4 space right foot. Patient did note some improvement with injection given previously." *Id*. The physical examination revealed "a forefoot cavus deformity bilateral." *Id*. There was "pain & swelling in the 4[th] space [of the] right foot." *Id*. It was noted that "[t]here is diffuse foot & ankle pain bilateral." *Id*. The plan noted that "patient does have pain in both shoulders. Recommend blood work to rule out systemic arthritis." *Id*. It was recommended that Petitioner have an MRI "due to patient's recurrent pain & swelling." *Id*. at 3. An MRI was done at Henry Ford Macomb Hospital on March 30, 2014. *Id*. at 5.

On March 28, 2014, Petitioner's bloodwork revealed an abnormally high rheumatoid

factor. Ex. 3 at 112. His C-reactive protein ("CRP") and erythrocyte sedimentation rate ("ESR") were normal, he had a negative anti-nuclear antibody ("ANA") screen, and his vitamin D was low. Ex. 3 at 14, 16, 18-20.

Petitioner returned to Shores Podiatry Associates on April 14, 2014 to review the results of the MRI. Ex. 6 at 4. The "subjective" portion of the record from the visit states, "Patient notes some continued pain in the right foot. Patient's blood work shows significant markers for rheumatoid arthritis." Ex. 6 at 4. The record also notes "Review MRI results. Advise patient that the MRI shows a soft tissue mass which may represent a rheumatoid nodule versus neuroma. Recommend surgical excision. Patient wishes to defer at this point due to need for further evaluation & initiation of treatment for the rheumatoid arthritis." *Id*. The radiology record from Henry Ford Macomb Hospital notes "3.2 cm soft tissue lesion that has a fourth metatarsals most consistent with a neuroma." *Id*. at 5.

On April 29, 2014, Dr. Timothy Brennan, a rheumatologist at the Shores Rheumatology, PC, examined Petitioner and opined on his condition. Ex. 3 at 101. Dr. Brennan wrote,

> In October of 2013, he recalls a day where his left heel was painful following which he developed significant pain and discomfort in both sets of metatarsal phalangeal joints. Over time, this progressed to involve both wrists, his metacarpal phalangeal joints, both elbows, and the left knee. He identifies mornings as his worst time but can't quantify the length of his stiffness…

Id. Under "[f]amily history," Petitioner indicated that "[h]e is unaware of anyone with connective tissue diseases or inflammatory arthritis." *Id*. Dr. Brennan noted that Petitioner was "judged as being a good historian." *Id*. at 102. The "[j]oint examination was significant for tenderness of both elbows," and "[h]e was tender at the right fourth PIP joint." *Id*. at 102. The examination also revealed "bony hypertrophy at both first metacarpal phalangeal joints" and it was noted that Petitioner was "significantly tender over all 5 of the right and left first metatarsal phalangeal joints." *Id*. Dr. Brennan concluded that Petitioner had "chronic signs and symptoms of an inflammatory, peripheral, symmetrical polyarthritis and a high titer positive rheumatoid factor consistent with rheumatoid arthritis," and that "[t]here is a soft tissue mass in the right foot between the fourth and fifth metatarsal phalangeal joints consistent with a neuroma on imaging." *Id*. Dr. Brennan "initiated treatment with 5 mg of prednisone per day." *Id*.

Petitioner followed up with Dr. Brennan on May 13, 2014. Ex. 3 at 104. Petitioner requested a second opinion at the University of Michigan. *Id*. The record notes that Petitioner "does not recognize any significant improvement since starting prednisone. He does complain specifically that his left elbow, left knee, and both ankles have become symptomatic." *Id*. Dr. Brennan wrote that Petitioner "is convinced that his rheumatoid disease was precipitated by receiving an influenza vaccine. It was his first and only vaccination. He has been reading online and states that prior to this he was 'perfectly healthy.' He informs me that he is 'talking to a lawyer.'" *Id*. The examination revealed "tenderness but no overt inflammatory synovitis, rashes, or nodules." *Id*. Dr. Brennan noted that "[Petitioner's] anti-CCP antibody return strongly positive at greater than 200 units per milliliter" and his impression was "Rheumatoid factor and anti-CCP positive rheumatoid arthritis." *Id*. at 105. Petitioner and his doctor "had a very lengthy discussion

about the disease, its etiology, prognosis, and therapeutic alternatives" and "[b]y the end of [their] discussion, he elected to begin treatment with methotrexate." *Id*. A return visit was scheduled for four weeks. *Id*.

On June 11, 2014, Petitioner returned to Shores Rheumatology. Ex. 7 at 65. Dr. Brennan noted that "[b]ecause he was feeling somewhat better, he has elected not to start methotrexate yet." *Id*. The record further indicates that "[Petitioner's] symptoms tend to be extremely variable. He has bad days where he feels fatigued and has diffuse joint pain and stiffness involving his ankles, feet, hands, and wrists. At other times he feels quite well. His morning stiffness tends to vary greatly." *Id*. Dr. Brennan noted that during the examination he "could not detect any active inflammatory synovitis although [Petitioner] does have multiple areas of joint tenderness." *Id*. The doctor's impression was rheumatoid disease and he planned to "resubmit the request for a second opinion at the University of Michigan." *Id*. at 66.

Petitioner met with Dr. Viju Moses, MBBS at the University of Michigan Rheumatology Clinic on September 2, 2014. Ex. 3 at 6. During that visit, Dr. Moses noted Petitioner's history:

> His symptoms started in Oct[ober] 2014, a few days after a flu shot. He first noted pain in the top of both feet. It was worse in the morning, and he had morning stiffness of 3-4 hours…Since Mar[ch] 2014 he started getting pain in his hands, w rists [sic], L[eft] shoulder, R[ight] knee and L[eft] buttock>R[ight] buttock. Unsure about morning stiffness for these joints…Fluctuating fatigue, sometimes severe.

Id. Additionally, "[a]t baseline [Petitioner] is involved in various sports and exercises, and continues to do so with difficulty. For example[,] hand symptoms impair playing basketball." *Id*. Petitioner reported to Dr. Moses that "more recently his hand pains have been bothering him again." *Id*. Bloodwork from that visit revealed a high Rheumatoid factor value of 476, noting the normal range as being 0-15 IU/mL, and a high cyclic citrullinated peptide antibody value of >250, noting the normal range as being 0-19 U/mL. *Id*. at 10. Dr. Moses concluded that these findings were "consistent with Rheumatoid arthritis." *Id*. at 12.

On October 31, 2014, a reading of Petitioner's September 2, 2014 MRI revealed "[f]ocal soft tissue enhancement along the dorsal web space between the fourth and fifth MTP joints, without definite bony erosions," with "possible associated fifth MTP synovial enhancement and perforation." Ex. 3 at 48. The records indicated that "[t]his could be compatible with focal synovitis given the patient's apparent history of rheumatoid arthritis, however, definite connection to the intra-articular soft tissue cannot be determined on current study." *Id*.

Petitioner went to Renaissance Plastic Surgery for excision of a nodule at the base of his glabella on December 11, 2014. Ex. 5 at 1. The medical history included "rheumatoid arthritis occurring after a flu shot." *Id*.

On December 30, 2014, Petitioner reported to Dr. Moses that "[h]is joint symptoms were well controlled till 2-3 weeks ago, after which he has been having increased joint pains, with no swelling but possible increased morning stiffness for 1-2 hours." Ex. 3 at 55. Dr. Moses noted Petitioner "has features of flare of RA with worsening of symptoms and morning stiffness." *Id*.

The plan was to increase his dose of methotrexate to 20mg per week. *Id*.

Petitioner returned to Dr. Moses on May 5, 2015. Ex. 3 at 67. The record notes that "[h]e currently has pain in the L[eft]>R[ight] shoulders. Has noted locking of the L[eft] 2nd digit a few times. R[ight] knee becomes painful with exercise. The balls of his feet are sometimes painful. There is no morning stiffness, but the L[eft] shoulder pain is better after exercise." *Id*. The musculoskeletal exam revealed "[m]ild tenderness in PIPs of hands with some synovial thickening. Mild tenderness in MCPs. Normal ROM. No palpable nodule adj[acent] to the L[eft] 2nd metacarpal. L[eft] elbow flexion deformity, milder on R[ight]." Dr. Moses decided to add Plaquenil and sulfasalazine "to prevent progression of joint damage." *Id*. at 69.

On May 11, 2015, Petitioner saw Dr. Guevara at Silver Pine Medical for "cold symptoms." Ex. 7 at 7. Joint problems, joint aches, and backache were noted under problem list. *Id*. On May 20, 2015, Petitioner returned to Silver Pine Medical for a physical. *Id*. at 3. The record notes that he "feels well with no complaints." *Id*.

On July 17, 2015, Petitioner spoke with a medical assistant over the phone about his lab results and reported that "the balls of his feet are really painful. He said his toes are not swollen or painful, just the balls of his feet. He also said that the knuckle of his ring finger on his left hand is also very painful. He also has pain that comes and goes in his shoulder." Ex. 3 at 81. Similarly, on August 10, 2015, Petitioner called Dr. Moses' office "with complaints of pain in his feet in the past month. Pain/swelling in balls of feet. Pain in hands Left > Right." *Id*. at 83.

On October 9, 2015, Petitioner called Dr. Moses' office again complaining that he had "painful and swollen feet that he can hardly walk. He state[s] that the methotrexate is not working and he do[es] not want to take Prednisone." Ex. 22 at 1. Later that day, Petitioner spoke with a resident in Dr. Moses' office, the record from which states, "[h]e is complaining of sever[e] bilateral feet pain and he is unable to walk comfortably. Two days ago he noted bilateral hand swelling and fingers locking o[n] him while driving. He stated that steroids not working for him and he has been on steroids for [t]he last year as well as methotrexate and sulfasalazine." *Id*. at 2.

Petitioner had a follow-up with Dr. Moses on March 22, 2016 noting "pain in multiple joints, including the MTPs, knees, shoulders, and PIP joints of hands. He notes morning worsening especially in the feet." Ex. 22 at 20. Dr. Moses noted Petitioner was "not willing to do any further vaccinations since he was concerned about the possibility of RA associated with a[n] influenza vaccine." Ex. 21 at 12.

On July 1, 2016, Janet Kennedy, RN spoke with Petitioner over the phone and reported:

> Patient started Humira approximately 2 months ago. After first injection he experienced lower back muscle stabbing pain that ended in 1-2 days. Following the first injection he reports that he has joint pain [in] shoulders L[eft]>R[ight], hips, hands and feet. He states that with each injection that the pain is getting worse and is not subsiding. He is having difficulty walking.[] Patient is also experiencing muscle spasms in lower back and calves that occurs 1-2 days after injection.

Ex. 22 at 31.

Petitioner spoke with Dr. Moses' office[3] over the telephone on September 6, 2016 and reported that "he has had pain in his hips for the past month and the pain is getting worse. Patient states it is really bad in his left hip and it is hard to cross his left leg." Ex. 22 at 36. A record of a telephone call later that day reads "for the past 1.5 months, he has been having significant pain in both of his hips, which is most severe in his left hip and accompanied by a loss of mobility. Patient states that the loss of mobility prevents him from running, and prevents him from doing daily tasks such as washing his feet in the shower. Patient states that he finds these symptoms very worrying . . ." *Id*.

A follow-up telephone call with Laurie Coppock, RN notes that she "[s]poke with pt and he is experiencing significant limitations to his ADLs. His left hip is the most severe. He can not lift to cross his legs and the pain is a 8-9/10 when walking. Pts left elbow has had a[n] increase in pain but it is his hip that he is very concerned with. Pt states that he 'feels like he has blown out his hip[.]' It just will not work anymore." Ex. 22 at 36. On September 7, 2016, records of a call with Dr. Jessie Alperin note that Petitioner "has severe pain in the left hip. He is not able to cross his leg. He has severe pain with walking. He does also note pain in the right hip, but not severe." *Id*. at 37.

III. Affidavits, Expert Reports, and Testimony

A. Petitioner's Affidavit

Within a day or two of the shot, Petitioner stated that he began experiencing swelling around his neck and jawline which continued about a week. Ex. 1 at ¶ 4. He also began to experience pain in the tops of both of his feet. *Id*. The foot pain, along with fatigue, malaise, and a general stiffness of his entire body, worsened in the early morning and lasted for a few hours. *Id*. In an effort to reduce the pain, Petitioner stated that he used over-the-counter medication with some benefit. *Id*. Petitioner thought that he was either getting a cold or the flu. *Id*. at ¶ 5. He was having continued foot pain and stiffness. *Id*. He was also experiencing nasal congestion and postnasal discharge. *Id*.

B. The Parties' Experts

1. Petitioner's Expert – Dr. Thomas Zizic

In support of his claim, Petitioner offered the medical expert opinion of Dr. Thomas Zizic. Dr. Zizic has been an Assistant and then an Associate Professor of Medicine at Johns Hopkins University School of Medicine in Baltimore, Maryland since 1973. Ex. 19 at 2 (hereinafter "Zizic CV"). He was also the Associate Director of the Rheumatic Disease Unit for Johns Hopkins at the Good Samaritan Hospital from approximately 1975 to 1985. *Id.* at 4.

Dr. Zizic is a founding fellow of the American College of Rheumatology. Zizic CV at 3.

[3] Records indicate Dr. Moses left the University of Michigan some time prior to September 6, 2016. Ex. 22 at 36.

He received his medical degree from Johns Hopkins University School of Medicine in 1965 and completed an internship and residency in internal medicine at Johns Hopkins University Hospital Center from 1965 to 1967. *Id.* at 1-2. From 1967 through 1969, Dr. Zizic served as a flight surgeon at the School of Aerospace Medicine at Brooks Air Force Base in San Antonio, Texas and from 1969 to 1971, he served as Post-Doctoral Fellow in Rheumatology at Johns Hopkins. *Id.* at 2.

In 1971, Dr. Zizic became an Instructor of Medicine and has remained on the faculty at Johns Hopkins University School of Medicine. Zizic CV at 2. For the first seventeen years, he was full-time faculty, after which he began serving part time upon entering into private practice in rheumatology. *Id.* at 6-7.

Dr. Zizic is former President of the Maryland Society of Rheumatic Disease and was on the National Committees of the Arthritis Foundation and the Lupus Foundation. Zizic CV at 3-4. He is also co-Founder of the National Osteonecrosis Foundation and currently on the Board of Directors of the National Center for Osteonecrosis Research and Education. *Id.* at 5-6.

Dr. Zizic's research has included osteoarthritis, osteoporosis, osteonecrosis, the study of connective tissue diseases including damage to cartilage and tendons and such disorders as systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, polymyositis and a variety of other diseases that have an immunologic basis. Zizic CV at 19-25. Dr. Zizic has published approximately 100 articles and abstracts as well as several dozen chapters in medical textbooks. *Id.* at 7-18.

Dr. Zizic authored a total of three reports in this case and testified during the entitlement hearing. Dr. Zizic opined that Petitioner's flu vaccine caused his RA.

2. Respondent's Expert – Dr. Mehrdad Matloubian

Respondent offered the medical expert opinion of Dr. Mehrdad Matloubian. Dr. Matloubian is a physician and Associate Professor of Medicine in the division of rheumatology at the University of California, San Francisco. Ex. B at 1 (hereinafter "Matloubian CV"). He has been on faculty at UCSF for approximately 20 years. Matloubian CV at 2. Dr. Matloubian is a board-certified and practicing rheumatologist. *Id.*

Dr. Matloubian also has a Ph.D. in virology/immunology and has been engaged in research in this area for more than twenty years. *See generally*, Matloubian CV. His areas of expertise include T and B cell responses, especially to viruses as well as factors that regulate lymphocyte circulation and trafficking. *Id.* at 2-3. Throughout most of his research career, he has focused on innate and adaptive immune responses, including those of T and B cells, to acute and chronic viral infections. *Id.* at 6-7. Dr. Matloubian has published peer-reviewed articles in both areas. *Id.* at 8-11.

Dr. Matloubian actively evaluates and treats patients with complex autoimmune diseases at a tertiary referral center and has a great interest in mechanisms of autoimmunity. Matloubian CV at 2. Tr. at 204-08. He is qualified to address both diagnostic and immunological issues regarding these diseases.

Dr. Matloubian authored a total of three reports in this case. He also testified during the entitlement hearing. Dr. Matloubian opined that Petitioner's vaccine was not the cause of his subsequently-diagnosed rheumatoid arthritis.

C. Expert Reports

1. Dr. Zizic's First Expert Report

Dr. Zizic authored a total of three reports in this case. Exs. 18, 49, 53. Dr. Zizic also testified at hearing. Dr. Zizic opined that Petitioner's flu vaccine was the cause of his subsequently-diagnosed non-erosive seropositive rheumatoid arthritis.

In Dr. Zizic's first report filed on October 27, 2016, he began by summarizing Petitioner's medical history and then provided his opinion and analysis. Ex. 18 at 1-16, (hereinafter "First Zizic Rep."). Dr. Zizic started out with an overview of the adaptive immune system and general immunological processes.

Dr. Zizic acknowledged that the etiology or cause of rheumatoid arthritis is still unknown. First Zizic Rep. at 18. However, there have been major advances in our understanding of the pathogenesis of RA. *Id*. He stated that currently, it is believed that RA develops in a "genetically susceptible individual in response to one or more environmental triggers." *Id*. Dr. Zizic said that infection and immunization, "whose function is to stimulate the immune system in order to protect against a specific infection," are considered among those environmental triggers and that "musculoskeletal symptoms (arthralgia, arthritis) may occur in response to different types of immunizations." *Id*.

Dr. Zizic pointed to studies by Harrison et al. (Ex. 36) and Symmons et al. (Ex. 37), which showed "48 of 898 (5.3%) patients with early inflammatory polyarthritis referred to the Norfolk Arthritis Register reported an immunization with tetanus toxoid or influenza in the six weeks prior to symptom onset." First Zizic Rep. at 19. He stated that "[t]he authors concluded that in a small number of susceptible individuals, immunization may act as a trigger for RA." *Id*.

Dr. Zizic went on to explain that this occurs when the "body's immune system produces antibodies to infectious agents or vaccines that cross-react with self-molecules," a process called molecular mimicry. First Zizic Rep. at 19. He stated that based on familial studies, it is believed that the HLA molecule plays a major role in the genetic-susceptibility component of RA. *Id*. (*citing* Deighton et al., *The contribution of HLA to rheumatoid arthritis*, 36 CLINICAL GENETICS, 178-82 (1989) (filed as Ex. 38); Jawaheer et al., "*Homozygosity" for the HLA-DR Shared Epitope Contributes the Highest Risk for Rheumatoid Arthritis Concordant in Identical Twins*, 37 ARTHRITIS & RHEUMATISM, 681-86, 1994 (filed as Ex. 39); Gregersen et al., *The Shared Epitope Hypothesis*, 30 ARTHRITIS & RHEUMATISM 1205-13, 1987 (filed as Ex. 40). Dr. Zizic stated that the HLA-DRB1 shared epitope found in RA patients is the result of "cross-reactivity and molecular mimicry with a pathogen." First Zizic Rep. at 19; *citing* Ollier et al., *Genetic epidemiology of rheumatoid disease*, 51 BRITISH MEDICAL BULLETIN 267-85, 1995 (filed as Ex. 29).

Dr. Zizic highlighted acute rheumatic fever as an example of molecular mimicry from infectious disease. First Zizic Rep. at 20. Streptococcus antigens cross-react with self-antigens resulting in inflammation in the joints, skin, brain, and heart causing acute rheumatic fever. *Id*. As an example of molecular mimicry in vaccine-induced autoimmune disease, Dr. Zizic pointed to Lyme vaccine, a protein which cross reacts with hLFA-1 self-molecules causing arthritis. *Id*. The Lyme vaccine has since been removed from the market. *Id*.

Dr. Zizic explained that humans have over ten billion B and T cell receptors, randomly developed and unique to each individual. First Zizic Rep. at 20. Some people have an effective immune response to vaccinations while others have no or an inadequate response. *Id.* Dr. Zizic stated that because of this vast repertoire and genetic heterogeneity, it would be unlikely that even large epidemiologic studies can capture the rare incidents of vaccine-induced autoimmunity. *Id.*

Dr. Zizic went on to describe research that demonstrates molecular mimicry between the influenza virus and a portion of the type II collagen ("CII") molecule as a mechanism by which the influenza vaccine can trigger autoimmunity. First Zizic Rep. at 20-21. An article by Sekine et al. highlights the importance of CII in RA pathogenesis. *See* Sekine et al., *Type II collagen is a target antigen of clonally expanded T cells in the synovium of patients with rheumatoid arthritis*, 58 ANN RHEUM DIS 446-50 (1999) (filed as Ex. 44). It has been shown that a CII peptide (256-271) contains epitopes that can trigger an RA-specific T cell response. *Id*. at 21 (*citing* Diab et al., *Human collagen II peptide 256-271 preferentially binds to HLA-DR molecules associated with susceptibility to rheumatoid arthritis*, 49 IMMUNOGENETICS 36-44 (1999) (filed as Ex. 45)). Dr. Zizic explained that influenza virus hemagglutinin 308-317 peptide shares a similar three-dimensional structure with CII 256-271 for purposes of molecular mimicry and can thus bind HLA-DR4/1 molecules with higher affinity. *Id.* Dr. Zizic stated that "[t]hus, it is logical that the influenza virus hemagglutinin peptide acts in a similar mean as the CII peptide, with respect to induction of [RA]." *Id*.

Dr. Zizic concluded that, with respect to the first prong of *Althen*, Petitioner's vaccination triggered activation of B and/or T lymphocytes through "molecular mimicry, cross-priming, immune complex formation or a combination of these, which because of Joseph Moran's genetic susceptibility, resulted in autoimmunity and the development of RA." First Zizic Rep. at 21. As to the second prong, Dr. Zizic explained that, (1) Petitioner did not have any symptoms prior to his vaccination, (2) his RA diagnosis was contemporaneously documented, and (3) he was found to be strongly seropositive. *Id*. Dr. Zizic then stated that other autoimmune diseases were excluded both clinically and after various tests. *Id*. He stated that "it is my opinion that this is a logical sequence of cause…and [] effect." *Id.* at 21-22. Finally, with respect to prong three, Dr. Zizic opined that "the petitioner developed RA symptoms within days after the influenza vaccination" and that "this is precisely the timeline that one would expect." *Id*. It is Dr. Zizic's opinion, "that the facts of this case support the view that Mr. Joseph Moran, more likely than not, developed new onset of RA as a result of the influenza vaccination." *Id*.

2. Dr. Matloubian's First Expert Report

In his first report filed on March 20, 2017, Dr. Matloubian highlighted a number of factors in support of his position that Petitioner's vaccine did not cause his condition. Ex. A (hereinafter

"First Matloubian Rep."). Petitioner was diagnosed with a neuroma in his foot several months after his influenza vaccination and subsequent bloodwork revealed abnormally high rheumatoid factor and anti-CCP antibodies. Dr. Matloubian stated that development of autoantibodies precedes clinical manifestation of RA by many years and that the environmental factors that trigger full-blown disease are not yet known. First Matloubian Rep. at 6-7. He pointed to various studies into the effects of vaccines in support of his theory that no causal relationship to RA has been established, including one which revealed no exacerbation of symptoms following immunization of RA patients with the influenza vaccine. *Id*. at 8.

Dr. Matloubian attributed Petitioner's rheumatoid arthritis to his history of smoking, calling it a "major major risk factor." First Matloubian Rep. at 16. He stated that smoking "has been strongly associated with seropositive RA." *Id*. Dr. Matloubian also suggested Petitioner's use of antibiotics could have led to the development of autoimmunity by affecting his gut microbiome and the balance of his immune system. *Id.*

Dr. Matloubian concluded that a link between the influenza virus and inflammatory arthritis has never been found, thus making it "implausible that an influenza vaccine would do so." First Matloubian Rep. at 16.

3. Dr. Zizic's Second Expert Report

In his second report filed on July 3, 2017, Dr. Zizic responded to Dr. Matloubian's first report. Ex. 49 (hereinafter "Second Zizic Rep."). First, he made clear that he agrees with Dr. Matloubian that deferral to the treating physicians with respect to diagnosis is appropriate. Second Zizic Rep. at 1. Most notably, he highlighted a recent study done by Firestein et al. *Id*.; Firestein et al., *Immunopathogenesis of Rheumatoid Arthritis*, 46 IMMUNITY 183-96 (2017) (hereinafter "Firestein") (filed as Ex. 50). Dr. Zizic explained that based on this article, it is believed that "RA starts with a high-risk genetic background." Second Zizic Rep. at 1. Dr. Zizic went on to quote that "[o]ne of the important lessons of this prolonged and stepwise pre-RA process is that the sequence of events does not require autoimmunity against the native protein in the earlier stages." *Id*. (*quoting* Firestein at 6).

Dr. Zizic reiterated "[i]t is still more likely that [Petitioner's] influenza vaccination, given in a temporally-appropriate time prior to his first manifestation of symptoms of RA, was the causative agent for the development of disease." *Id*.

4. Dr. Matloubian's Second Expert Report

In his second report filed on July 25, 2018, Dr. Matloubian responded to Dr. Zizic's second report. Ex. C (hereinafter "Second Matloubian Rep."). Dr. Matloubian reiterated that "the disease process starts years before" clinical manifestation of rheumatoid arthritis in the form of joint pain or swelling. Second Matloubian Rep. at 1. Dr. Matloubian stated that "immunological processes that led to the petitioner's development of RA were going on for years before he presented with joint pain and was diagnosed with RA." *Id*. at 2.

Dr. Matloubian cited an ongoing clinical trial exploring whether treatment of asymptomatic

people with positive anti-CCP antibody can prevent the future development of clinical RA. Second Matloubian Rep. at 2. The rationale behind the study, he stated, is that "individuals with elevation of anti-CCP greater than 2 times the normal value have approximately a 50% chance of developing RA within 3 years." *Id*.

In addressing Dr. Zizic's theory of molecular mimicry, Dr. Matloubian cited to Firestein: "'more than 90% of patients with RA express one of the variants of HLA-DR4." *Id*. at 2. Dr. Matloubian argued that if Dr. Zizic's molecular mimicry theory were true, then one would expect to see a greater incidence of influenza vaccine or infection-related exacerbation of symptoms in this genetically susceptible group. He stated that "based on medical literature and multiple studies…1) influenza infection does not lead to development of an autoimmune arthritis similar to RA; 2) influenza vaccination is not associated with development of RA even in those who have HLA-DR4, also known as HLA-DRB1; and 3) patients with RA do not have worsening of their disease after an influenza vaccination." *Id*. at 3. Dr. Matloubian indicated that this is strong evidence against an association between influenza antigens and the subsequent development of RA via molecular mimicry. *Id*.

5. Dr. Zizic's Third Expert Report

In his third and final report filed on July 1, 2019, Dr. Zizic responded to specific questions I posed of each party's expert. Ex. 53 (hereinafter "Third Zizic Rep.").

In response to my first question, Dr. Zizic opined that elevated levels of serum inflammatory markers, such as the erythrocyte sedimentation rate ("ESR") and CRP, are not necessary criteria in the diagnosis of RA. Third Zizic Rep. at 1. He highlighted a study of 9,135 active RA patients by Kay et al. that revealed approximately "58% had neither elevated ESR nor CRP." *Id*. at 1-2. He also pointed out that elevated acute phase response accounts for 1 point among the criteria for RA, "only a small component contributing to the classification criteria." *Id*. at 2. Dr. Zizic added that "[i]f they were a requisite component of the criteria the majority of patients with [RA] would no longer qualify for the diagnosis" as suggested by the Kay study. *Id*. at 3.

I then asked Dr. Zizic what symptom(s) he considered to be Petitioner's clinical manifestation of onset. In response, Dr. Zizic stated that "[w]ithin days of the flu vaccination on October 17, 2013, Mr. Moran apparently developed pain on the top of his feet, fatigue, malaise and generalized morning stiffness lasting 2 hours." Third Zizic Rep. at 4. He went on to say, "[t]he most frequent joints involved in rheumatoid arthritis are the small joints of the hands or the feet." *Id*. In Dr. Zizic's opinion Petitioner's onset of RA was this joint pain and stiffness days following vaccination. *Id*.

Finally, in response to my third question regarding medical feasibility of the timing of onset, Dr. Zizic responded that "[t]he…progression from onset in a localized area such as small joints of the feet to involvement of multiple joints with a [sic] 'inflammatory peripheral symmetric polyarthritis, high titer rheumatoid factor, consistent with rheumatoid arthritis' over approximately six months is a very typical course in the development and progression of rheumatoid arthritis." Third Zizic Rep. at 4.

6. Dr. Matloubian's Third Expert Report

Dr. Matloubian's third and final report was filed on July 22, 2019, responding to specific questions I posed of each party's expert. Ex. D (hereinafter "Third Matloubian Rep.").

In response to my first question, Dr. Matloubian expressed skepticism regarding Petitioner's diagnosis due to unremarkable physical exams in April and May 2014. Third Matloubian Rep. at 1. Ultimately, however, he deferred to Petitioner's treating physicians with respect to his diagnosis of non-erosive seropositive RA. *Id*. at 2.

With respect to my second question regarding symptom onset, Dr. Matloubian stated that the medical records are unclear and they do not "provide any documentation [that] either physician observed joint swelling or instances of it being reported by the petitioner himself." Third Matloubian Rep. at 2. Dr. Matloubian stated that Petitioner's treaters at the University of Michigan noted "pain in other joints, including hands and wrists and buttocks since 3/2014." *Id*. As such, Dr. Matloubian put onset "sometime in '3/2014.'" *Id*.

Finally, I asked Dr. Matloubian for his opinion regarding the significance of the fact that Petitioner quit smoking more than 15 years prior to onset/diagnosis. He stated that that fact would have no effect on his assessment. Third Matloubian Rep. at 3. Dr. Matloubian cited to an article by Malmström et al., *The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting*, Nature Reviews | Immunology, 1-16 (2016) (hereinafter "Malmström") (filed as Ex. A-5) to support his argument that smoking is a high-risk factor in the development of RA. *Id*. He explained that since RA is thought to go through multiple pre-clinical phases years prior to clinical presentation, Petitioner's smoking would have led to a breakdown in tolerance resulting in autoimmunity. *Id*. Dr. Matloubian concluded "once this breakdown of tolerance has been triggered by smoking in a genetically susceptible person, it can continue to progress to full blown clinical RA even if that person quits smoking." *Id*.

D. Expert Testimony

1. Dr. Zizic's Testimony

Dr. Zizic testified during the entitlement hearing. I recognized him as an expert in the fields of immunology and rheumatology. Tr. at 14.

During his testimony, Dr. Zizic discussed several pieces of medical literature filed in support of Petitioner's case. According to Dr. Zizic, the Norfolk Arthritis Registry was created in the United Kingdom in order to "look at early polyarthritis to see what it evolved into." Tr. at 23. (*see* Symmons & Harrison, *Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature*, BRITISH SOCIETY FOR RHEUMATOLOGY, 2000 (filed as Ex. 37) (hereinafter "Symmons")). In discussing this article, Dr. Zizic highlighted the authors' note, stating "there is evidence that tetanus and influenza immunizations may trigger RA in susceptible hosts." Tr. at 29, *citing* Symmons at 5.

Dr. Zizic testified that "In the NOAR case-control study there was an association between immunization in the 6 weeks preceding symptom onset and the development of rheumatoid arthritis. (Odds ratio, 2.4; 95 percent confidence interval)" -- and they did overlap one, so it's not totally statistically significant, just suggested". Tr. at 29-30.

Dr. Zizic also discussed the Ray article. *See* 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 6592-97 (2011), (filed as Ex. A Tab 19) (hereinafter "Ray"). Dr. Zizic testified that Ray demonstrated a 36 percent increased likelihood of developing rheumatoid arthritis within the 180 days after influenza vaccination as compared to unvaccinated individuals. Tr. at 44. Dr. Zizic also took issue with the authors' findings, because the cohort analysis found a "possible association" between RA and the influenza vaccine in the previous 180 and 365 days; however, in the case-control analysis, "cases were no more likely than controls to have received any of the three vaccines." Ray at 6592; Tr. at 36. Dr. Zizic testified that the authors in Ray improperly diluted the study with controls, which changed the results. He stated:

> You can't, because you don't like the results of your initial study, go back and include patients that you excluded from the study initially for very good reasons. And, now, you're going to put them back in and you put three times as many patients in as controls -- as compared to vaccinations? So if there's a background rate, which there is, for rheumatoid arthritis, you put three times as many controls with the background rate that's the same as the vaccinated rate, and now the difference you've found is no longer statistically significant, which is exactly what happened here in a post-hoc analysis, which is totally scientifically wrong.

Tr. at 38.

Dr. Zizic testified about similar concerns about the validity of the Bengtsson study. He stated,

> This is not a valid study because all of your cases, virtually, that occur after vaccination are going to occur within the first year. And so let's say you have a 25 percent increase in the first year. If you add four more years to both groups, now you've spread that 25 percent out over five years and it's 5 percent. And so that you have so many more -- you've diluted that so that it's not significant anymore when you add four more years of observation.

Tr. at 389-90.

Dr. Zizic also discussed the Wang article. *See* Wang et al., *Vaccinations and risk of systematic lupus erythematosus and rheumatoid arthritis: A systemic review and meta-analysis*, 16 AUTOIMMUNITY REVIEWS 756-65 (2017) (filed as Ex. 58) (hereinafter "Wang"). According to Dr. Zizic, this article "definitively shows influenza vaccination … can cause rheumatoid arthritis in some patients." Tr. at 46. Specifically, Dr. Zizic testified that the meta-analysis showed that "there was a 36 percent increased chance of developing rheumatoid arthritis if you got vaccination versus no vaccination." Tr. at 48.

After discussing the literature that supports Petitioner's position that flu vaccine can cause RA, Dr. Zizic testified in more detail about the specifics of his molecular mimicry theory.

Dr. Zizic began by defining some terms. He stated that Type II collagen "is the collagen that is specific for cartilage and it is much more durable and resistant to load bearing". Tr. at 55. He testified that type II collagen is one of the major autoantigens in RA. *Id.* at 56. "[W]e find antibodies to type II collagen not only circulating in the blood, but in the synovial fluid, bathing the lining of the joints in rheumatoid arthritis, and those immune complexes cause activation of the complement inflammatory system and cause damage to the joints and release the cytokines." *Id.*

Dr Zizic defined influenza virus hemagglutinin as "a portion of the viral protein in influenza viruses, part of the viral antigen." Tr. at 61. Influenza virus hemagglutinin is also present in the influenza vaccine.

Dr. Zizic opined that molecular mimicry is a reasonable theory by which vaccination with the influenza vaccine can cause RA. He opined that the literature demonstrates that both type II collagen and the wild type influenza virus hemagglutinin can be recognized and activated by the same type II collagen specific T cell clones from patients with rheumatoid arthritis. Tr. at 169-70. When asked whether any of the medical literature specifically indicates that the same T cell can be activated by both the collagen peptide and the influenza HA peptide, Dr. Zizic testified as follows:

> Well, as we talked about earlier, I think when you're looking at the Sun article, the type II collagen and the hemagglutinin peptide both activated T cells and you could inhibit them by the altered hemagglutinin peptide. If you want to read that, we can go back to that article. That's the one -- not every article is going to get what you want, but that one says it best, I think.

Tr. at 125-26.

He further testified as follows:

> both of them activate the T cell because they're cross-reacting here. And that activated T cell from that clone of T cells for rheumatoid arthritis patients and peripheral blood lymphocytes, that activation can be induced by either one. What more do you want for molecular mimicry?

Tr. at 127.

Dr. Zizic discussed the onset of symptoms of RA in Petitioner's case. He opined that Petitioner's first symptom of RA was the pain and swelling in his feet. Tr. at 72, 81. He described plantar foot pain as pain in the area under the sole and the arch of the foot. *Id.* at 99. He opined that pain in this region was consistent with RA because "not only do the joints get involved, sometimes the tendon sheaths get inflamed. And so you can have generalized pain in that plantar

fascia area where the tendons are attaching to the small bones of the toes, the MTP joints, which is the ball of the foot." Tr. at 173-74.

In support of this position, Dr. Zizic discussed Petitioner's January 16, 2015 medical appointment. He testified that Dr. DeYoung determined, "there was moderate pain and tenderness -- a moderate pain to palpation, which is tenderness. She called it arthritis and then injected with Dexamethasone." Tr. at 103; Ex 6 at 1.

Dr. Zizic testified that an onset of symptoms two days following vaccination is a medically appropriate interval. His opinion was premised on a recall response. He stated, "one may have had exposure to that same antigen in previous influenza injection vaccination that weren't sufficient to cause effector T cells to form but were sufficient to activate memory T cells, which on re-exposure would cause a more rapid -- a stronger response than the first exposure." Tr. at 81. Dr. Zizic further opined that a prior flu infection could have caused the brisk response as well. *Id.* Dr. Zizic also testified that if I were to find that onset of Petitioner's RA took place in March (five months after vaccination), that this interval is also consistent with his theory of molecular mimicry. He based this opinion on the Ray study. Tr. at 406-07.

Dr Zizic also testified about the presence of anti-CCP antibodies prior to diagnosis. He opined that antibodies may be present, but it is unknown what percentage of patients develop these antibodies before they develop clinical RA. Tr. at 114. He discussed the Nielen study, stating, "they actually went back in the pool of individuals searching for antibodies in existence prediagnosis and only half of that entire group had antibodies - therefore, the other half developed them later or acutely." Tr. at 178; *see also* Nielen et al., *Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis*, 50 ARTHRITIS & RHEUMATISM 2, 380-86, 2004 (filed as Ex. A-8) (hereinafter "Nielen"). He discussed the results from other studies, which similarly indicated percentages demonstrating the presence of anti-CCP antibodies prior to diagnosis as below 50%. Tr. at 179.

2. Dr. Matloubian's Testimony

Dr. Matloubian also testified at the entitlement hearing. I recognized him as an expert in the fields of rheumatology and immunology. Tr. at 209-10. Dr. Matloubian provided his opinion that the flu vaccine did not cause Petitioner's RA. Tr. at 237. This opinion is based on several factors. Dr. Matloubian testified that RA is a relatively common disease which typically starts between the ages of 50 and 75. *Id.* In addition, Petitioner has an established risk factor for RA, which was his prior history of smoking. *Id.* Further, given the millions of doses of flu vaccine administered every year, the flu vaccine is not associated with RA in the studies that have been conducted. *Id.* at 237-38. Finally, Dr. Matloubian noted that The American College of Rheumatology recommends flu vaccine for people with RA. *Id.* at 238.

a. *Studies on Flu Vaccine and RA*

Dr. Matloubian testified about various studies concerning the flu vaccine and RA. He discussed Singh et al., *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*, ARTHRITIS & RHEUMATOLOGY, 1-25, 2015, (filed as Ex A Tab 25)

(hereinafter "Singh"). Dr. Matloubian testified that this article concludes that the flu vaccine is recommended for people with RA. Tr. at 291-92.

Dr. Matloubian also discussed Westra et al., *Vaccination of patients with autoimmune inflammatory rheumatic diseases*, 11 RHEUMATOLOGY 135-45, 2011 (filed as Ex A Tab 24) (hereinafter "Westra"). Dr. Matloubian described Westra as "a comprehensive review on safety of different types of vaccines in people with autoimmune rheumatic diseases" Tr. at 292. He testified the article concluded that RA patients; "don't have increased disease activity or flare of their disease" after flu vaccine. Tr. at 293; Westra at 140.

Dr. Matloubian also discussed the Bengtsson study. *See* Bengtsson et al., *Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study*, 69 ANN RHEUM DIS 1831-33, 2010 (filed as Ex. A-20) (hereinafter "Bengtsson"). Bengtsson is a case-control study, which Dr. Matloubian defined as a study with two populations, one with a disease and one without. The study determines whether "the population who had disease ha[d] more exposure to a risk factor than the population that did not have disease." Tr. at 297. According to Dr. Matloubian, the study found that "vaccinations neither increased the risk of RA overall, so odds ratio was one, no risk, and it wasn't significant, nor the risk of two major subgroups of RA, antibody citrullinated peptide positive, or ACPA positive, and ACPA negative disease." *Id.* at 298.

Dr. Matloubian also testified about the Ray article, and specifically addressed the issues with the study raised by Dr. Zizic. He began by discussing the difference between cohort and case control studies generally.

> So in a cohort study, what you do is you don't look at the disease, you don't start with people who have the disease, you start with exposure. So you pick a group that are exposed to potential risk factor and a group that is not exposed to that potential risk factor, you follow them over time, and you ask, wait, did the exposed group have higher incidence of the disease versus the nonexposed group, and if they did, that says that being exposed is a risk factor or, you know, provides a relative risk. An example of this would be smoking. So you can start with a group of smokers and a group of nonsmokers, and then you follow them over time and then you see if one of them developed rheumatoid arthritis more than the other group.

Tr. at 304. With respect to the study itself,[4] Dr. Matloubian opined that the principles employed by the authors was not improper, as alleged by Dr. Zizic. He noted that in Ray, they only had between 300 and 400 subjects, so they added more data to their analysis. Tr. at 306. Dr. Matloubian opined that "in case-control studies, it's absolutely okay to have up to three or four controls per cases. What this allows you to do is to increase the statistical power of the study and the precision of the study. So there is nothing wrong and it's not frowned upon to use three to four times controls for case-control studies." *Id.* at 307. Dr. Matloubian further noted that a case control analysis looks at an odds ratio, which is a proportion. As a result, it does not matter "how many controls you add,

[4] Dr. Matloubian also noted that the time intervals in the Ray study were based on the date RA symptoms began and not (as Dr. Zizic claimed) on the date of diagnosis. Tr. at 305.

because you're not looking at absolute numbers of people who developed RA, you're looking at the proportion of patients who developed RA." Tr. at 412-13. In other words, adding additional subjects into the sample size doesn't dilute the numbers.

The Ray study concluded that the relative risk of getting RA after flu vaccination was .72. Tr. at 309. Dr. Matloubian testified this means "there's no risk to getting RA based on this within the first 90 days after influenza immunization. And basically 95 percent confidence interval across 1." *Id.*

Dr. Matloubian also discussed the medical literature filed by Petitioner in support of his claim. He discussed the Harrison article which was part of NOAR (Norfolk Arthritis Register). *See*, Harrison et al., *Patients Who Develop Inflammatory Polyarthritis (IP) after Immunization are Clinically Indistinguishable from Other Patients with IP*, 36 BRITISH JOURNAL OF RHEUMATOLOGY, 366-69, 1997 (filed as Ex. 36) (hereinafter "Harrison"). Dr. Matloubian noted that the sample size of this study was particularly small and further that not all of the patients studied had seropositive RA. Tr. at 294. "So table 4, which is on page 3, it's a little bit difficult to get the exact numbers. So they have multiple columns in this table, the nonimmunized, immunized and then influenza immunized. So total number of people who got influenza vaccine is only 15. Just 15. So their conclusion is based on 15 people." Tr. at 294., *referencing* Harrison at 3. Dr. Matloubian further noted that of these 15 people with a clinical diagnosis of RA, only three of them were rheumatoid factor positive. "And when they compare to the group that was nonimmunized with 32 percent of rheumatoid factor positive, there is no statistical difference between the influenza immunized and nonimmunized group." Tr. at 295. With respect to the finding of this study, Dr. Matloubian stated, "the difference they see is not statistically significant because the odds ratio is from 0.45 to 5.4. It crosses one." *Id.* at 296.

Dr. Matloubian also discussed Symmons and the conclusion cited by Dr. Zizic: "Similarly, there's evidence that tetanus and influenza immunization may trigger RA in susceptible hosts" (*citing* Symmons at 5). Dr. Matloubian noted that this statement cites to reference 62, which is the Harrison paper. Tr. at 300. Dr. Matloubian reiterated that in the Harrison paper, only 15 people received the influenza vaccine, and the results did not reach statistical significance. *Id.* He concluded by stating that "there was really no indication there to support an association between influenza vaccination and development of RA." *Id.*

Dr. Matloubian testified about the Wang article. According to Dr. Matloubian, because Wang is a meta-analysis, "the quality of [the study] depends on the quality of the original papers, how they manipulate the data, what they think is important, what's not important." Tr. at 310. Because of this, Dr. Matloubian testified that the quality of a meta-analysis can be variable. *Id.*

Specifically, Dr. Matloubian referred to table 1, which depicts the five articles that relate to influenza vaccination and RA; Bengtsson, Ray, Ho, Persson, and Vaughn. When citing to Ray, the Wang meta-analysis only discussed the cohort part of the study, not the case control portion, so, according to Dr. Matloubian, "they're being selective in what part of the data they're analyzing." Tr. at 311. Dr. Matloubian additionally noted that Persson involves the Pandemrix vaccine, which he described as an "unusual influenza vaccine that's been associated with narcolepsy, and it's not the one that's used in the U.S." *Id.* In summarizing the data studied by Wang, Dr. Matloubian

testified that "of those, the only one that's statistically significant is the Ray one, the cohort part of it, and possibly the Persson, which is the pandemrix." *Id.* at 313.

b. *Molecular Mimicry Theory*

Dr. Matloubian defined molecular mimicry as a process that occurs "when the same T cell receptor recognizes two different peptides bound to the same MHC molecule." Tr. at 269. He explained that the part of the peptide that interacts with the MHC molecule is called "anchor residue of the peptide." *Id.* at 268. The part of the peptide that is recognized by the T cell is called the "T cell contact residue of a peptide" *Id.* at 269. He further testified that "two different peptides can share the anchor residues and bind to the same MHC molecule, but they could be different in their T cell contact residue and bind to different T cell receptors. *Id.*

Dr. Matloubian testified that none of Petitioner's medical literature demonstrated that the same T cell can recognize both influenza peptide and collagen peptide in association with HLA-DR4. Tr. at 275-76.

Dr. Matloubian opined that the criteria used to establish the applicability of a molecular mimicry theory is set forth in one of Petitioner's exhibits, authored by Dr. Schattner. *See* A. Schattner, *Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines*, 23 VACCINE 3876-86, 2005 (filed as Ex. 25) (hereinafter "Schattner"). He testified about these criteria as follows:

> [T]he specific virus infection should be linked to a specific autoimmunity. So in this case, is influenza virus infection specifically linked to development of rheumatoid arthritis.
>
> Second is there has to be some mechanism or mechanisms where exposure to the viral antigens during infection or vaccination leads to autoimmunity, and one has to establish that mechanism. So in this case, is there any evidence to support molecular mimicry between influenza-associated antigens and RA-associated antigens.
>
> And then there has to be some evidence that people who have vaccinated with this vaccine developed an autoimmune disease.

Tr. at 277-78, *citing* Schattner at 3881.

Dr. Matloubian noted that there is no evidence that the flu virus is associated with RA. "So if there was any molecular mimicry, and especially at the level of T cells that would lead allegedly to flu vaccine causing rheumatoid arthritis, one should be able to see that with flu infection itself". Tr. at 238. He further opined that RA is not considered to be a post-infectious autoimmune disease. *Id.* at 253.

> And, in fact, you know, people who are actively doing research on T cell responses in patients with rheumatoid arthritis and they are specifically looking at T cell

> responses to antigens associated with rheumatoid arthritis, they use flu-associated antigens and responses to those antigens as a control.
>
> So if they thought that there was molecular mimicry, especially at the T cell level, between flu antigens and RA-associated antigens, why would they use flu antigens as a control? And the reason they do is because there aren't -- the scientists don't think there is molecular mimicry between them.

Tr. at 239.

c. *RA Begins Years before Clinically-Apparent Disease*

Dr. Matloubian made the point that pre-clinical RA begins years before it become clinically apparent. He testified that "it's important to note that people who do research on pathogenesis of RA and are writing about its natural history believe that rheumatoid arthritis doesn't begin overnight, that it takes years for it to become clinically apparent." Tr. at 256. He cited to several pieces of medical literature in support of this position. *See e.g.*, Deane & Holers, *The Natural History of Rheumatoid Arthritis*, 41 CLINICAL THERAPEUTICS 7, 1256-69, 2019 (filed as Ex. H) (hereinafter "Deane & Holers") (noting that RA-related autoantibodies are detectable in the circulation a mean of three to five years before the clinically detectable inflammatory arthritis). *See also*, Tr. at 255.

d. *Smoking and RA*

Dr. Matloubian testified that smoking is an established environmental risk factor for RA. Tr. at 319-20. Although Petitioner quit smoking 17 years before he developed RA, Dr. Matloubian opined that "the insult" of smoking had still taken place. *Id.* at 250. In support of his position, Dr. Matloubian referred to Liu. *See* Liu et al., *Impact and timing of smoking cessation on reducing risk for rheumatoid arthritis among women in the Nurses' Health Studies*, 71 ARTHRITIS CARE RES 7, 914-24, 2019 (filed as Ex. G) (hereinafter "Liu"). He noted that Liu "reached the conclusion that a mono state elevated RA risk was still detectable 30 years after quitting smoking." Tr. at 250-51. In response to Petitioner's point that the study only involved women, Dr. Matloubian noted that the findings in Liu also discussed "other studies that include men and women with similar findings." *Id.* at 374.

e. *The Onset of Petitioner's RA*

Dr. Matloubian testified with respect to the onset of Petitioner's RA that "his joint pains that are more consistent with possible rheumatoid arthritis started sometime in March of 2014." Tr. at 237. He disputed Petitioner's point that he reported foot pain consistent with RA soon after vaccination. Specifically, Dr. Matloubian testified that heel pain and plantar pain are not consistent with or typical of RA. Tr. at 383. Pain in balls of the feet is a typical manifestation of RA, but Dr. Matloubian noted that Petitioner described the tops of feet as being on fire, which is not the same thing as the balls of the feet. Tr. at 322-23. Further, Dr. Matloubian made the point that the balls of Petitioner's feet could have been hurting because he was walking on them due to his heel pain. *Id.* at 382.

Dr. Matloubian also noted that when Petitioner went to the podiatrist, he described pain which turned out to be a neuroma. Further "on the MRI, it did not show bone marrow edema or inflammation in a lot of -- in all the MTP joints." Tr. at 383. Dr. Matloubian opined that if Petitioner had RA, one would expect to see bone marrow edema and synovitis on MRI:

> You would expect to see bone marrow edema in the -- so MTP is the joint, but the bone across the MTP is called the phalanx, so you would see bone marrow edema in the phalanx, or in the metatarsal, and you would see synovitis, which is basically inflammation of the synovial tissue. But even that can sometimes be nonspecific because you can get synovitis from osteoarthritis and trauma.

Id. Dr. Matloubian noted the MRI did not reveal evidence of bone marrow edema or inflammation. *Id.*

In discussing Petitioner's affidavit, Dr. Matloubian acknowledged that Petitioner reported fatigue, malaise and general stiffness which seemed to be worse early in the morning and lasted for a few hours. However, he noted that he was,

> trying to reconcile that on the March 5th visit with Dr. Guevara when he says he's feeling fine, energetic, exercises multiple times a week. And so I'm just trying to see, you know, if this is happening a few days after his immunization, but four months later he's doing well, and is not complaining of morning stiffness and exercising well. So I'm just trying to reconcile those.

Tr. at 323. For these reasons, Dr. Matloubian opined that Petitioner more likely than not developed RA in March 2016 and not several days after vaccination.

IV. Applicable Law

A. Petitioner's Burden

Under the Vaccine Act, a petitioner may prevail in one of two ways. First, a petitioner may demonstrate that he suffered a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the time period provided in the Table. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

For both Table and non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010); *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting*

v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records of by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*. *Althen* requires that petitioner establish by preponderant evidence that the vaccinations he received caused her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

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

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs*., 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility … in many cases may be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish her overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Hum. Servs*., 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, because they are created contemporaneously with the

treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

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

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013). *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs*., 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral

testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013).

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

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

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

a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

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

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate persuasiveness and reliability of expert testimony has routinely been upheld. *See*, e.g., *Snyder*, 88 Fed. Cl. at 743. In this matter, (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in

evaluating petitions for compensation under the Vaccine Act").

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all of the medical literature in detail, I have reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

V. Analysis

A. Rheumatoid Arthritis Generally

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes joint inflammation, pain, and degeneration. Deane & Holers at 1256. Its pathogenesis is incompletely understood. First Matloubian Rep. at 7. If left untreated, RA leads to loss of physical function and ability to perform and carry out daily tasks. Scott et al., *Rheumatoid arthritis*, 376 LANCET 1094-1108, 2010 (filed as Ex. A-13). RA is a disease that affects peripheral joints typically in the hands, wrists, and feet. Tr. at 16; First Matloubian Rep. at 6. Those affected experience over 30 minutes of morning joint stiffness. *Id.* Two different type of RA include seropositive and seronegative RA. *See* Malmström at 1. Seropositive RA is the more common of the two, affecting two-thirds of the RA population. *Id.* In order to be classified as having seropositive RA, an individual has anti-CCP antibodies. Tr. at 214.

The incidence of rheumatoid arthritis is approximately 24 per hundred thousand per year. *See* Ahmed at 6. Dr. Matloubian testified that based on these numbers, you would expect 55,000 new cases of RA in the U.S. each year. Tr. at 316; Ahmed at 6.

The American College of Rheumatology's ("ACR") 2010 RA classification criteria provide an established guide for the diagnosis of RA:

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Aletaha et al., *Rheumatoid Arthritis Classification Criteria*, 62 ARTHRITIS & RHEUMATISM 2569 (2010) (filed as Ex. A-4). On a scale of 0 to 10, a score of 6 or greater is indicative of "definite RA." *Id.* An involved joint is any joint with swelling or tenderness on examination that is indicative of active synovitis. *Id.* at 8. Small joints include the wrist and various joints in the hands and feet. *Id.* at 9. Large joints are defined as the shoulders, elbows, hips, knees and ankles. *Id.*

Patients typically experience both pre-clinical and clinical phases. Deane & Holers at 1256. The pre-clinical phase, during which visible symptoms are not present, may last several years prior to onset of clinically diagnosable signs of joint disease. *Id.* at 1257.

B. Petitioner's Diagnosis

On April 29, 2014, Petitioner visited rheumatologist Dr. Timothy Brennan and reported to him that foot pain started in October 2013. Ex. 13 at 7. The pain then progressed to include his wrists, hands, elbows and his left knee. Petitioner reported that the pain and stiffness were worse in the morning. *Id.* During a May 13 follow-up visit, Dr. Brennan noted a strongly positive anti-CCP antibody result and the impression was RF-positive and anti-CCP-positive RA. Ex. 7 at 67.

Petitioner obtained a second opinion from Dr. Viju Moses at the University of Michigan Rheumatology Clinic on September 2, 2014. Ex. 3 at 6. Dr. Moses reviewed Petitioner's record and determined that the findings were consistent with RA.

Petitioner's expert, Dr. Zizic agrees with the treating rheumatologists that Petitioner has RA. Dr. Matloubian also testified that he believes Petitioner's correct diagnosis is seropositive rheumatoid arthritis. Tr. at 234. As a result, I find that Petitioner has provided sufficient evidence to show that more likely than not, he suffers from seropositive RA.

C. *Althen* Prong One

In the context of the Program, "to establish causation, the standard of proof is preponderance of evidence, not scientific certainty." *Langland v. Sec'y of Health & Hum. Serv.*, 109 Fed. Cl. 421, 441 (Fed Cir. 2013). Petitioner's burden under *Althen*'s first prong is to provide a medical theory causally connecting the vaccination and the injury. *Id.* This theory must be sound and reliable. *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019). For the reasons discussed in detail below, I find that Petitioner has not provided a sound and reliable medical theory causally connecting flu vaccination to RA.

Petitioner filed the Schattner article which delineates three criteria that must be met in order to establish a role for viral vaccines in the development of autoimmunity. These criteria are:

> *First,* virus infections should be linked to autoimmunity. *Second, a* mechanism or mechanisms whereby exposure to viral antigens (be it during infection or vaccination) leads to autoimmunity must be established. *Third,* evidence must be obtained that patients who have been vaccinated against viruses developed an autoimmune disease, bearing in mind that association alone does not necessarily indicate causality.

Schattner at 3881. Both experts generally endorsed these criteria during the entitlement hearing (except as noted below with respect to Dr. Zizic). *See* Tr. at 151, 277-78. I have used them as a framework in evaluating Petitioner's *Althen* prong one theory.[5]

1. There is not an Established Connection between Flu Virus and RA

Dr. Matloubian opined that there is no established connection between the flu virus and RA. First Matloubian Rep. at 16. He testified that

> this allegation that flu vaccine could cause rheumatoid arthritis is illogical because, you know, flu virus infection itself has not been associated with rheumatoid arthritis. And the antigens that are in the flu vaccine are also in the wild-type flu virus. So if there was any molecular mimicry, and especially at the level of T cells that would lead allegedly to flu vaccine causing rheumatoid arthritis, one should be able to see that with flu infection itself[.]

Tr. at 238-39. Dr. Zizic also agreed with the position that there is no evidence of an association between flu virus and RA. He testified as follows at the entitlement hearing:

> **Q:** Is there data that de novo wild flu infection causes RA?

[5] While I have used the criteria outlined by Schattner as a way to organize the *Althen* prong one analysis, I understand that petitioners are not required to demonstrate a specific biologic mechanism which caused their disease, nor are they required to present medical literature or epidemiological studies in support of their theory. *See Kottenstette*, ---Fed. Appx.---, 2021 WL 2434329 (Fed. Cir. June 15, 2021) (reaffirming the principle that "proof of causation does not 'require identification and proof of specific biological mechanisms[.]'" *citing Knudsen*, 35 F.3d at 549; *Andreu,* 569 F.3d at 1378-79.

A: No, not that I'm aware of.

Tr. at 152. Accordingly, both experts agree on this point. However, Dr. Zizic contended that Dr. Schattner's first criterion is inapplicable to this case; he testified that "if you['ve] got evidence that the vaccine causes it, you don't need evidence that infection causes it." *Id.* at 151. The reason Dr. Zizic provided in support of this opinion is that it is too difficult to measure whether a viral infection causes a disease because viral infections are very common and "[p]eople don't remember those details" in terms of onset of illness. *Id.* Dr. Zizic did generally agree that if the flu vaccine causes RA, then the virus should as well. *Id.* at 152-53. His issue with the first criterion appeared to be the ability to accurately measure and study the question.

I note this this position articulated at hearing is a departure from the position expressed in his first expert report. When citing to Schattner in that document, Dr. Zizic opined that Schattner's first criterion meant that some viral infections should cause some form of autoimmunity generally. He stated,

> With respect to the first condition, it is clear that some viral and microbial infections result in autoimmune diseases. Evidence exists for the association of streptococcus pyogenes infection with the development of rheumatic fever, *Trypanosoma cruzi* parasitic infection and Chagas disease cardiomyopathy, the spirochete *Borellia burgdorfii* [sic] and Lyme disease, *Campylobacter jejuni* infection and Guillan-Barre [sic] syndrome and Ebstein-Barr [sic] virus and multiple sclerosis.

First Zizic Rep. at 17. As noted above, Dr. Zizic did not advance this position at hearing, and instead testified that the first criterion was unnecessary because the second had been satisfied.

I do not find Dr. Zizic's position on this issue to be persuasive. There are several notable examples of specific viral infections that have been linked to disease. *See* First Matloubian Rep. at 12 ("natural infection with the measles virus may lead to thrombocytopenia. Therefore, when thrombocytopenia (ITP) occurs after immunization with MMR, IOM considers it an adverse event due to the vaccine."); s*ee also*, Terry L. Moore, MD, *Pathogenesis and diagnosis of viral arthritis,* UPTODATE, 2016 (filed as EX. A-17) for examples filed in this case (*noting* "the most common viruses causing arthritis and arthralgias are parvovirus, hepatitis B, hepatitis C, rubella, Epstein-Barr virus, and the alphaviruses."). Medical literature filed in the Vaccine Program is also replete with examples of studies that involve infection. Additionally, it seems counterintuitive that Dr. Schattner would include as her first criterion a connection that could not be studied or established. Accordingly, I decline to credit the position that it is too difficult to measure whether a viral infection can cause a condition. The evidence preponderantly demonstrates that there is not an established connection between the flu virus and RA.

2. Petitioner's Molecular Mimicry Theory is not Sound and Reliable in this Particular Case

In this case, Dr. Zizic has opined that the flu vaccine can cause RA through the process of molecular mimicry. Pursuant to this theory, the structure of a foreign invader mimics the structure

of cells in the body. This similarity causes the immune system to produce antibodies that attack the host.

Before discussing the specifics of Dr. Zizic's theory, it is important to define some terms. The purpose of the T cell is to eradicate infections and to activate other cells (such as macrophages and B lymphocytes). Abbas et al., CELLULAR AND MOLECULAR IMMUNOLOGY, Elsevir, 9th ed. 2018, at 117 (filed as Ex. E) (hereinafter "Abbas"). Each T cell has a unique T cell receptor; when a T cell sees a peptide and it is a peptide the T cell recognizes, it becomes activated. (figure 4, A-5). The immune response is triggered due to the T cell's ability to recognize a specific peptide. *Id.*

Antigen presenting cells (APC) are the cells that "capture antigens and display them to T lymphocytes." Abbas at 117. MHC molecules are found on the surface of antigen presenting cells and display "host cell-associated antigens for recognition by $CD4^+$ and $CD8^+$ T cells." *Id.*

HLA-DR4 is "a human HLA or MHC molecule" and "certain alleles of it called the shared epitope have been associated with risk of seropositive rheumatoid arthritis." Tr. at 271. Influenza virus hemagglutinin is "a portion of the viral protein in influenza viruses." Tr. at 61. It is also present in the influenza vaccine. *Id.* at 61-62.

Type II collagen is an important structure involved in the pathogenesis of RA. Tr. at 56. The collagen II peptide binds to HLA-DR molecules, which are associated with susceptibility to RA. As Dr. Matloubian stated in his report, "Many autoimmune diseases are associated with a specific HLA molecule. … specific alleles of HLA-DR (class II molecule) are associated with the development of rheumatoid arthritis." First Matloubian Rep. at 9.

In the present case, Dr. Zizic has opined that molecular mimicry between a portion of the flu virus molecule and a portion of type II collagen caused Petitioner to develop RA.

Dr. Zizic described a specific viral antigen (influenza virus hemagglutinin 308-317 peptide) and how it can bind to HLA-DR4. He also identified the collagen II autoantigen (CII 256-271) which can also bind to HLA-DR4. The influenza virus hemagglutinin 308-317 peptide shares a similar structure with CII 256-271 and both can bind to HLA-DR4 molecules. Sun et al., *Superior Molecularly Altered Influenza Virus Hemagglutinin Peptide 308-317 Inhibits Collagen-Induced Arthritis by Inducing CD4+ Treg Cell Expansion*, 64 ARTHRITIS & RHEUMATISM 7, 2158-68, 2012 (filed as Ex. 47) (hereinafter "Sun"). Based on this, Dr. Zizic opined that "it is logical that the influenza virus hemagglutinin peptide acts in a similar manner as the type II collagen peptide, with respect to the induction of rheumatoid arthritis." First Zizic Rep. at 21.

Dr. Matloubian defined molecular mimicry as a process that occurs "when the same T cell receptor recognizes two different peptides bound to the same MHC molecule." Tr. at 269. He explained that the part of the peptide that interacts with the MHC molecule is called "anchor residue of the peptide." *Id.* at 268. The part of the peptide that is recognized by the T cell is called the "T cell contact residue of a peptide". *Id.* at 269.

Dr. Matloubian referred to the following figure to illustrate these points:

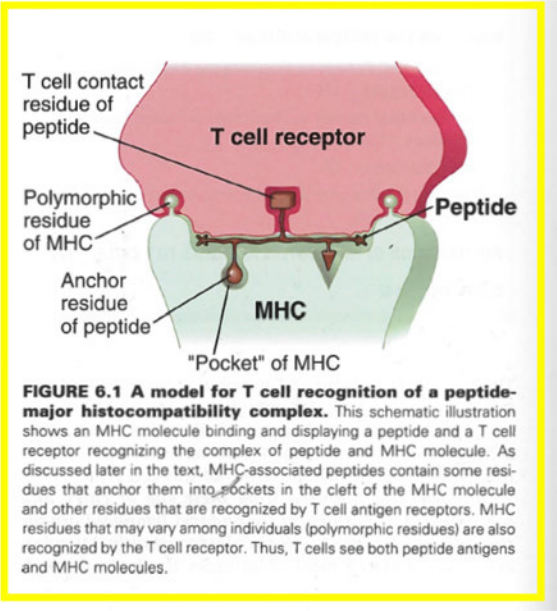


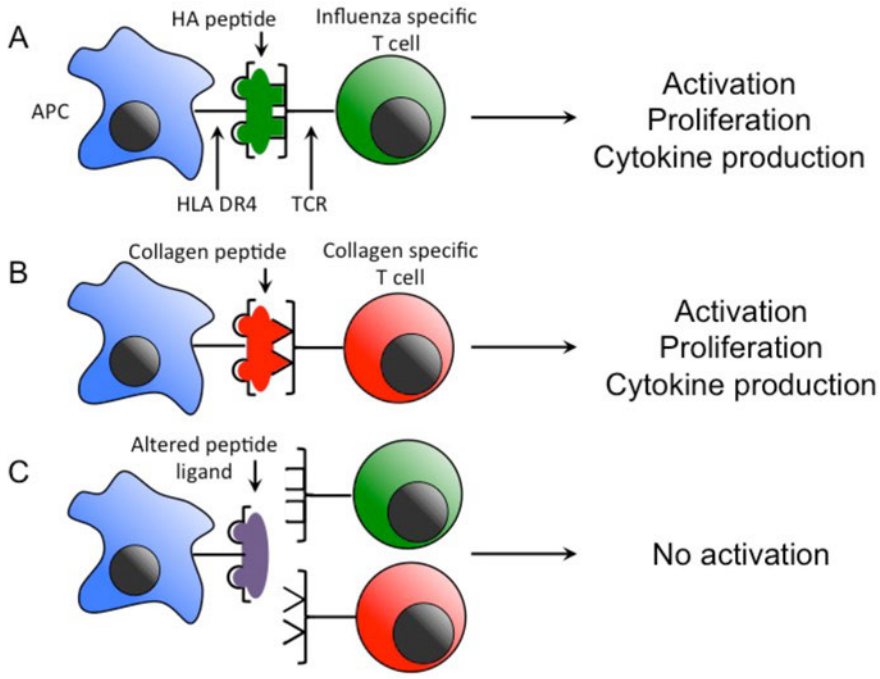
FIGURE 6.1 A model for T cell recognition of a peptide-major histocompatibility complex. This schematic illustration shows an MHC molecule binding and displaying a peptide and a T cell receptor recognizing the complex of peptide and MHC molecule. As discussed later in the text, MHC-associated peptides contain some residues that anchor them into pockets in the cleft of the MHC molecule and other residues that are recognized by T cell antigen receptors. MHC residues that may vary among individuals (polymorphic residues) are also recognized by the T cell receptor. Thus, T cells see both peptide antigens and MHC molecules.

Abbas at 5. He further testified that "two different peptides can share the anchor residues and bind to the same MHC molecule, but they could be different in their T cell contact residue and bind to different T cell receptors. *Id.*

In explaining how molecular mimicry works, Dr. Matloubian used an analogy to Legos. In his analogy, the MHC molecule is represented by a flat Lego sheet; the peptides are different figurines; and the T cells are represented by different children that only like one type of figurine. Tr. at 262-63. Dr. Matloubian noted that each figurine can fit onto the main Lego platform. Similarly, MHC molecules bind to many different peptides. Dr. Matloubian further opined that a peptide binding to an MHC molecule does not constitute molecular mimicry; instead, molecular mimicry occurs when the same T cell (child) becomes activated (interested) by more than one peptide (Lego figurine). *Id.* He testified: "And that's what the T cells are. They are really highly specific for one peptide and they get excited or activated when they see that peptide. MHC is just there to provide the platform for the T cells." Tr. at 263.

Dr. Matloubian does not contest that HLA-DR4 can bind to an influenza-derived peptide as well as a collagen-derived one. First Matloubian Rep. at 14. In his view, the question that remains unanswered by any literature Petitioner filed is "can the same T cells recognize both type II collagen peptide and influenza HA peptide bound to HLA-DR4?" *Id.* at 14. In other words, can T cells be activated by both peptides? This is important because the ability of T cells to recognize two different antigens is the definition of molecular mimicry. Without this T cell involvement, there is no mimicry. Tr. at 271.

In order to further elucidate this issue, Dr. Matloubian presented a model of the bonds that exist between an antigen presenting cell and a T cell.



First Matloubian Rep. at 15. The first bond is between the antigen presenting cell and the antigen (either flu or collagen). The second bond is between the antigen and the T cell.

During the hearing, Dr. Zizic agreed that molecular mimicry occurs at the level of the T cell but testified that the articles filed by Petitioner demonstrate that either type II collagen or influenza virus hemagglutinin are able to activate and bind with the same T cells. Tr. at 70.

Dr. Zizic cited to a specific portion of the Sun article to support his position that the same T cells recognize both type II collagen peptide and influenza HA peptide. Sun wrote,

> In our previous studies, we designed an altered hemagglutinin antigen 308-317 peptide with amino acid substitutions at sites of T cell receptor contact (YAKQATLALA). In vitro, the altered HA 308-217 peptide inhibited T cell activation induced by wild hemagglutinin antigen 308-317 peptide and wild type II collagen 263-272 peptide in the collagen II specific T cell clones and peripheral lymphocytes in patients with rheumatoid arthritis.

Sun at 2159. Dr. Zizic testified that "obviously, those T cell clones and peripheral lymphocytes from patients with rheumatoid arthritis activated T cells. Both of them did." Tr. at 126.

Dr. Matloubian testified that Dr. Zizic's interpretation of this portion of the Sun article was incorrect. He explained that the authors of Sun altered the T cell contact residue of the influenza peptide. Tr. at 284. Then when they inducted with a peptide that binds to HLA-DR4, it was not recognized by the T cell receptor of the influenza specific T cells because the T cell contact residue had been altered. *Id.* "[T]hey're hoping, because this peptide has higher affinity than the collagen peptide, that it will stay in there and block the collagen peptide from binding to the same HLA-DR4, and as a way, they will stop the response of the T cell to that collagen peptide." Tr. at 284.

In fact, the Sun authors concluded that this process suppressed the severity of CIA (collagen induced arthritis), and as a result, the altered peptide ligand could be a "promising candidate" in RA treatment. Sun at 2158.

Dr. Matloubian testified "basically what they are designing here is something that sits in the HLA-DR4 molecule and sits much tighter so that the collagen peptides don't bind. Nothing about molecular mimicry, nothing about cross-reactivity, nothing about the same T cell receptors seeing the same antigen." Tr. at 286-87. Dr. Matloubian's interpretation of the Sun article appears to be correct. The Sun authors are specifically addressing the contact between the HLA-DR4 molecule and peptides, not whether the same T cells recognize both type II collagen peptide and influenza HA peptide. The latter would constitute support for molecular mimicry, the former does not.

I am similarly convinced that the Skinner article does not stand for the proposition that the same T cell can recognize and become activated by both the type II collagen peptide and influenza HA peptide. *See* Skinner et al., *Lymphocyte responses to DRl/4 restricted peptides in rheumatoid arthritis, 53* ANN RHEUM DIS, 171-77, 1994 (filed as Ex. 48) (hereinafter "Skinner"). Similar to Sun, the authors in Skinner made an altered peptide ligand that binds to HLA-DR4 which in turn prevented the collagen-specific T cells from responding to it. *See generally*, Skinner; Tr. at 288. Dr Matloubian again noted, "There's no molecular mimicry, there's no showing of the same T cell receptor sees both collagen or hemagglutinin." *Id.* I again agree with Dr. Matloubian's assessment. In sum, the articles cited by Petitioner do not demonstrate that the same T cells can recognize both type II collagen peptide and influenza HA peptide bound to HLA-DR4. Thus, these articles to not support Petitioner's molecular mimicry theory. *See also Tullio v. Sec'y of Health & Hum. Servs.*, No. 15-51V, 2019 WL 7580149, at *22 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (also concluding that Petitioner had not established a viable molecular mimicry theory in his flu-RA case), *aff'd* 149 Fed. Cl. 448 (2020).

a. *Studies Use T Cell Reactivity to Influenza Virus Antigens as a Control*

The Malmström article is a review article discussing the pathogenesis of RA. In describing the article, Dr. Matloubian testified that "patients who have seropositive RA have T cells that are specific for [certain] citrullinated peptides." Tr. at 290. He then pointed to one sentence in Malmström which reads: "A parallel analysis in HLA-matched healthy controls showed much lower levels of T cell activation against these antigens, whereas reactivity to an unrelated antigen (from influenza virus) was similar between healthy controls and patients with RA." Malmström at 7. Dr. Matloubian noted that "when they're studying patients with rheumatoid arthritis and comparing presence of unreactive T cells relevant to RA, between the RA patients and the healthy controls, they are using T cell reactivity to antigens from influenza virus, an unrelated antigen, as a control." Tr. at 290-91.

The important point that Dr. Matloubian made was as follows:

> So scientists, researchers who are studying specifically T cell responses to rheumatoid arthritis using state-of-the-art technology believe that influenza virus antigens are unrelated to rheumatoid arthritis antigen, and that's why they can use

> them as controls. So they don't believe there's any molecular mimicry between rheumatoid arthritis antigens and influenza-associated antigens.

Tr. at 291. I find this point is persuasive evidence which further undermines Petitioner's position that molecular mimicry between a portion of the flu virus molecule and a portion of type II collagen caused Petitioner to develop RA.

Based on the foregoing analysis, I find that Petitioner's proffered prong one theory, molecular mimicry, is not a sound and reliable theory that the flu vaccine *can cause* RA.

3. The Majority of Persuasive Studies do not Support a Connection between Flu Vaccine and RA

Several large studies have been performed to assess whether the flu vaccine causes rheumatoid arthritis. Each study indicates that there is not an association between the two.

Epidemiologic evidence is relevant with respect to *Althen* prong one. *See, e.g., D'Tiole v. Sec'y of Health & Hum. Servs.,* 2016 U.S. Claims LEXIS 2003 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *mot. for review den'd*, 132 Fed. Cl. 421 (2017); *Blackburn v. Sec'y of Health & Hum. Servs.*, No. 10–410V, 2015 WL 425935, at *28–30 (Fed. Cl. Spec. Mstr. Jan. 9, 2015). However, this type of evidence is not required in order for a petitioner to establish that a vaccine can cause an injury. A vaccine injury is a rare event that cannot be disproved because a vaccinee did not experience a response consistent with that of the general population. *See Harris v. Sec'y of Health & Hum. Servs.*, No. 10–322V, 2014 WL 3159377, at *11 (Fed. Cl. Spec. Mstr. June 10, 2014) (finding that epidemiologic studies cannot absolutely refute causal connections, because it is possible that a larger study could always detect an increased risk), *mot. for review dismissed*, 2015 U.S. App. LEXIS 7921 (Fed. Cir. 2015).

Respondent presented several studies in support of his position that the flu vaccine does not cause RA. The Ray study was discussed extensively by both experts. This study involved a medical chart review of approximately one million subjects in Kaiser Permanente from 1997 through 1999 and included both a cohort analysis and a case-control analysis. In Ray, the cohort analysis found a possible association between the flu vaccine and RA in windows approximately six months and one year after flu vaccination. The researchers in Ray then increased the power of the study and conducted a larger case-control analysis. Ultimately, this study concluded that there was no risk of getting RA after flu vaccination. Ray at 6596.

Although Dr. Zizic criticized the case control portion of his study for diluting the sample size of the cohort, Dr. Matloubian persuasively testified that adding more cases should help to confirm existence of findings by increasing the power of the study. He stated,

> … if there was a true difference, if there was a true difference, an association between … influenza vaccine and development of RA, you would I think, if you bring more people, more people with RA who were vaccinated, and, you know, you would see that difference, but the fact that they could not reproduce … this finding and [the] fact that other studies that are well controlled didn't show this association,

> really puts into question actually the cohort analysis rather than the case-control analysis.

Tr. at 355. Setting aside the case control portion of Ray's findings, even the cohort analysis found there is no increased risk of RA within 90 days of flu vaccination. Ray at 6594. Petitioner seemingly relies on the Ray cohort findings which note a potential association between flu vaccine an RA within 180 days of vaccination. Any initial evidence of an association (which was later not borne out) is not persuasive in establishing that flu vaccine can cause RA when that association is so far removed from the date of vaccination. I find that the Ray study provides strong evidence that there is not an association between flu vaccine and RA.

I have also considered the Bengtsson case-control study. This study followed 1998 cases of RA and 2252 controls for five years after vaccination. Bengtsson did not find any association between the development of seropositive or seronegative RA and prior vaccine exposure. ("Vaccinations neither increased the risk of RA overall (OR 1.0, 95% CI 0.9 to 1.1) nor the risk of two major subgroups of RA (antibodies to citrullinated peptide-positive (ACPA-positive) and ACPA-negative disease)). Bengtsson at 1831. This study also provides persuasive evidence that flu vaccine is not associated with RA.

Respondent additionally presented the Fomin study. *See* Fomin et al., *Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNFα blockers*, 65 ANN RHEUM DIS, 191-94, 2006 (filed as Ex. A-22) (hereinafter "Fomin"). Fomin assessed the safety of flu vaccine in patients already diagnosed with RA. The results of this study indicated that "Vaccination against influenza was not associated with a significant worsening of any clinical or laboratory index of disease activity." Fomin at 193.

The Westra authors reported on six studies which addressed the safety of the flu vaccine in patients with autoimmune rheumatic diseases, to include RA. The authors stated that "no significant influence of vaccination on disease activity has been reported." Westra at 140.

Petitioner cited to several medical articles in support of his position that the flu vaccine can cause RA. One such paper is Basra et al., *Rheumatoid Arthritis and Swine Influenza Vaccine: A Case Report*, CASE REPORTS IN RHEUMATOLOGY, Vol. 2012, doi:10.1155/2012/785028 (filed as Ex. 52) (hereinafter "Basra"). Although Basra is a case report involving the H1N1 vaccine, the authors noted that "Vaccinations that are suspected to cause RA include influenza, MMR, HBV, tetanus toxoid, typhoid, paratyphoid A and B (TAB), polio, diphtheria, and smallpox." Basra at 1. This quotation references Schattner for support. *See id.* at 2. However, as Dr. Matloubian noted at hearing, Schattner concludes that "whenever you do controlled trials, you don't really find that these vaccines cause autoimmune diseases." Tr. at 342. Accordingly, this one sentence in Basra (a case report relating to a different vaccine) is substantially undermined.

Petitioner also cited to the Symmons study. The authors of this study stated that "there is evidence that tetanus and influenza immunization may trigger RA in susceptible hosts." Symmons at 5. Dr. Zizic testified that "In the NOAR case-control study there was an association between immunization in the 6 weeks preceding symptom onset and the development of rheumatoid arthritis. (Odds ratio, 2.4; 95 percent confidence interval)" -- and they did overlap one, so it's not

totally statistically significant, just suggested". Tr. at 29-30. In fact, the confidence interval is listed in the paper as "0.2, 23.2". Symmons at 5. If a confidence interval overlaps one, it is not statistically significant. *See* Tr. at 48-49; 296. Additionally, this statement cites to reference 62, which is the Harrison paper. In Harrison, only 15 people received the influenza vaccine, and the results did not reach statistical significance. Harrison at 3; Tr. at 294-95.

Petitioner also submitted the Wang article, which Dr. Zizic described as "a very key article that definitively shows influenza vaccination causes -- can cause rheumatoid arthritis in some patients." Tr. at 46. Wang is a meta-analysis, which means that the authors evaluated studies that have already been performed. Wang addressed five articles that relate to influenza vaccination and RA; Bengtsson, Ray, Ho, Persson, and Vaughn. When citing to Ray, the Wang meta-analysis only evaluated the cohort part of the study, not the case control portion. *See* Wang at 759. The fact that the authors in Wang chose to only include data that was contrary to the original study's finding undercuts Wang's persuasiveness.[6] While Bengtsson and Ray have been filed as exhibits in this case, the other studies referenced in Wang have not. Dr. Matloubian did note that Persson involves the Pandemrix vaccine, which is not used in the United States. It is difficult to draw conclusions about the other two studies referenced in Wang. In summarizing the data studied by Wang, Dr. Matloubian testified that "of those, the only one that's statistically significant is the Ray one, the cohort part of it, and possibly the Persson, which is the [P]andemrix." Tr. at 313.

Ultimately, in evaluating the medical literature filed in this case, the weight of the evidence suggests that there is not an association between flu vaccine and RA. Although I have considered Petitioner's filings, I have credited the larger studies (Ray, Bengtsson, Fomin, and Westra) over case reports, studies that do not reach statistical significance, and the Wang article.

4. Production of RA Auto-Antibodies

Also undercutting Petitioner's prong one theory is the point that a growing body of medical literature indicates that autoantibodies precede clinically apparent symptoms of RA by a period of years. According to Dr. Matloubian, the predominant thought within the rheumatological community is that autoantibodies exist within years of a seropositive RA diagnosis. He testified as follows:

> And, you know, between Dr. Zizic and I, we have submitted 10 review articles on rheumatoid arthritis and pathogenesis of rheumatoid arthritis, and they all say that

[6] Also undercutting the persuasiveness of this article is the author's reference to "ASIA" (Autoimmune syndrome induced by adjuvants) in their very first paragraph, calling it "a well defined auto-immune condition caused by adjuvants." Wang at 757. The ASIA theory for adjuvant-induced autoimmunity has not been deemed medically reliable in prior Program cases. *See, e.g., Monzon v. Sec'y of Health & Hum. Servs.,* No. 17-1055V, 2021 U.S. Claims LEXIS 1269, at *26 n.6 (Fed. Cl. Spec. Mstr. June 2, 2021); *see also Morris v. Sec'y of Health & Hum. Servs.,* No. 12-415V, 2016 WL 3022141, at *12 (Fed. Cl. Spec. Mstr. Apr. 1, 2016) (discussing lack of reliability of ASIA theory)*; Rowan v. Sec'y of Health & Hum. Servs.,* No. 10-272V, 2014 WL 7465661, at *16 (Fed. Cl. Spec. Mstr. Dec. 8, 2014*), mot. for review den'd*, 2015 WL 3562409 (Fed. Cl. May 18, 2015); *D'Angiolini v. Sec'y of Health & Hum. Servs.*, No. 99-578V, 2014 WL 1678145, at *60 (Fed. Cl. Spec. Mstr. Mar. 27, 2014), *mot. for review den'd*, 122 Fed. Cl. 86 (2015), *aff'd*, 645 F. App'x 1002 (Fed. Cir. 2016).

> it takes years for rheumatoid arthritis to develop. It doesn't happen overnight. It's … not like you get an infection or a vaccine and the next day you develop rheumatoid arthritis. This is years in the making.

Tr. at 247.

Some of the medical literature filed in this case supports this position. Deane & Holers in their 2019 article state that, "there is now established and evolving research that supports the conclusion that RA-related autoimmunity and inflammation are present long before the first onset of IA during a period that can be termed pre-RA." Deane & Holers at 1257. The authors further note that studies involving the history of RA "have found that RA-related autoantibodies are detectable in the circulation a mean of 3-5 years before the first clinically detectable IA." *Id.*

Petitioner correctly noted at hearing that in examining the data, only a percentage of patients studied tested positive for RA autoantibodies in the years prior to their diagnoses. This suggests that a percentage of patients who go on to develop clinical RA may not develop autoantibodies prior to the clinical onset of their disease. Deane & Holers make this point when they state, "although existing studies suggest that a high percentage of individuals who develop RF and/or ACPA-positive RA will have seropositivity of these antibodies before IA [inflammatory arthritis], not all individuals who develop IA have detectable seropositivity for autoantibodies preceding their arthritis." Deane & Holers at 1265. This statement is consistent with the other evidence Respondent filed in this case. *See* Malmström (noting that "ACPAs [antibodies to citrullinated protein antigens] and RF [rheumatoid factor] are often present in the blood long before any signs of joint inflammation"); Nielen (stating the production of antibodies "occurred in only half of the patients before onset of symptoms"); van Steenbergen et al, *The Preclinical Phase of Rheumatoid Arthritis,* 65 ARTHRITIS & RHEUMATISM 9, 2219-32, 2013 (filed as Ex. A-12) (stating that "In the Swedish study, the presence of IgM-RF and ACPA was reported in 19.3% and 33.7%, respectively, of the RA cases within 10 years before RA diagnosis, compared to 6.0% and 1.8%, respectively … Similarly, in the Dutch data set, 27.8% of the patients were IgM-RF positive and 40.5% were ACPA positive within 15 years prior to RA diagnosis").

Petitioner's point, that not all patients who go on to develop clinical RA have pre-existing autoantibodies is correct. Accordingly, this belief held by members of the rheumatology community that autoantibodies precede clinically apparent symptoms of RA, standing alone, does not eviscerate Petitioner's *Althen* prong one theory. However, it is some evidence that I have considered in ultimately concluding that Petitioner has not met his burden under *Althen's* first prong. Ultimately, I find it significant that "the researchers who publish articles on this believe that autoantibody and autoimmune disease that results in rheumatoid arthritis starts years before somebody clinically develops disease, not within days or months." Tr. at 330-31.

In considering the totality of the evidence discussed above, I find that Petitioner has not presented preponderant evidence in the form of a sound and reliable theory that the flu vaccine can cause RA.

D. *Althen* Prong Two

Under *Althen*'s second prong, a petitioner must "prove a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." *Id.* A petitioner is not required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Id.* (omitting internal citations). *Capizzano*, 440 F.3d at 1325. Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second *Althen* prong.

The incidence of rheumatoid arthritis is approximately 24 per 100,000 per year. *See* Ahmed at 6. Dr. Matloubian testified that based on these numbers, one would expect to see 55,000 new cases of RA in the U.S. each year. Tr. at 316. Dr. Matloubian used these data to estimate the number of people who would develop RA after vaccination through chance alone. If approximately 140 million people receive the flu vaccine each year, approximately 1,600 people would be expected to develop RA within six weeks of receipt of the flu vaccine through chance alone. *Id.* at 315-16. These data lend some support for the oft-cited principle in the Vaccine Program that temporal association alone does not suffice to demonstrate causation. *See, e.g.*, *Zumwalt v. Sec'y of Health & Hum. Servs.*, No. 16-994V, 2019 U.S. Claims LEXIS 465 at *59 (Fed. Cl. Spec. Mstr. Mar. 21, 2019), *aff'd*, 146 Fed. Cl. 525 (2019).

1. Petitioner's Evidence

Dr. Zizic summarized Petitioner's evidence in support of the second *Althen* prong. He stated,

> With respect to the second requirement, the petitioner did not have any persistent rheumatic symptoms prior to vaccination. There is nothing in the medical records to support any pre-existing autoimmune disease, nor any inflammatory form of arthritis, nor anything to suggest RA. The history subsequent to immunization clearly was contemporaneously documented as RA and was strongly seropositive with respect to both rheumatoid factor and CCP. Other autoimmune diseases were excluded on clinical grounds as well as immunological laboratory studies (e.g. ANA, ENA, C3, C4, ANCA, SCL 70, Jo 1). Thus it is my opinion that this is a logical sequence of cause (the influenza vaccine was the only perturbation to his immune system around the time of illness onset) and the effect (the development of RA). There is an absence of any other good explanation for a triggering event.

First Zizic Rep. at 21-22. In essence, Dr. Zizic has opined that Petitioner did not have RA before his flu vaccine, he developed RA after his flu vaccine, and there is no explanation for Petitioner's condition, so the influenza vaccine *did cause* Petitioner's RA. Although Dr. Zizic noted that Petitioner's RF and anti-CCP antibodies were "strongly seropositive", he did not explain whether or how this point demonstrates that Petitioner's flu vaccine likely caused his RA. The Federal Circuit in *Capizzano* noted that "[t]he second prong of the *Althen* ... test is not without meaning." *Capizzano*, 440 F.3d at 1327. Indeed, in *Althen*, the Court stated: "Although probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a

simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278.

2. Treating Physicians

In weighing evidence, special masters are expected to consider the views of treating doctors. *Cappizano*, 440 F.3d at 1326. The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. *See McCulloch v. Sec'y of Health & Hum. Servs.*, No. 09-293V, 2015 WL 3640610, at *20 (Fed. Cl. Spec. Mstr. May 22, 2015).

In this case, no treating physician persuasively attributed Petitioner's RA to his flu vaccine. This is not surprising, as the cause of RA is unknown. *See* First Zizic Rep. at 18 (noting that "despite major advances in our understanding of the pathogenesis of rheumatoid arthritis, the etiology remains unknown"). I note that one of Petitioner's records, from December 11, 2014 states under past medical history: "Includes rheumatoid arthritis occurring after a flu shot." Ex. 5 at 1. There is also a handwritten note later in this record which states "RA from flu shot". *Id.* at 3. I do not find that these notes provide a persuasive connection between the flu vaccine and Petitioner's RA. In fact, they read more as a history provided by Petitioner than as a medical opinion.[7]

3. Petitioner Had a History of Smoking

Petitioner was a former smoker who smoked "0.25 packs/day for 15 years." Ex. 3 at 7. The medical records are clear that Petitioner quit smoking approximately 17 years before the onset of his RA. *See* Ex. 13 at 7 (noting, "He smoked cigarettes until June 17, 1997 and none since."); Ex. 23 at 2, ("Has not smoked since 6/7/1997."); Ex. 51 at 2.9. (indicating Petitioner was a former smoker with a quit date of 1/1/1997 and that he smoked 0.25 packs/day for 15 years).

It is also clear that smoking is an established risk factor for RA. *See* Malmström at 2 (noting that smoking has a large impact on ACPA-positive patients); McInnes & Schett, *The pathogenesis of rheumatoid arthritis*, 365 N ENGL. J MED. 23, 2205-19, 2011 (filed as Ex. A-1) (stating that "Smoking and other forms of bronchial stress (e.g., exposure to silica) increase the risk of rheumatoid arthritis among persons with susceptibility HLA–DR4 alleles"); Hunt & Emery, *Defining populations at risk of rheumatoid arthritis: the first steps to prevention*, RHEUMATOLOGY,

[7] Several other medical records discuss Petitioner's RA in the context of his vaccination, but none persuasively link his vaccination to his RA; indeed, these records do not discuss a causal relationship between the two. For example, on September 2, 2014, a treating physician noted, "Symptoms started in Oct 201[3], a few days after a flu shot. *See* Ex. 3 at 6, 85, Ex. 7 at 57, Ex. 51 at 63. On May 13, 2014, it was noted that Petitioner "is convinced that his rheumatoid disease was precipitated by receiving an influenza vaccine. It was his first and only vaccination. He has been reading online states that prior to this he was 'perfectly healthy'. He informs me that he is 'talking to a lawyer.'" Ex. 7 at 67, Ex. 13 at 10, 37, Ex. 51 at 95. On September 10, 2016, Petitioner refused a flu vaccine because "he was concerned about the possibility of RA associated with an influenza vaccine." Ex. 21 at 12. On August 9, 2017, a history taken from Petitioner noted that: "Relevant background history begins in Oct 2013 a few days after patient received a flu shot: he first noted pain in the top of both feet that was worse in the morning and associated with morning stiffness of 3-4 hours." Ex. 51 at 32, 48.

Vol. 10, 521-30, 2014 (filed as Ex. A-7) (observing that smoking is a risk factor for seropositive RA).

While Petitioner concedes the fact that he has a history of smoking and that smoking generally is an established risk factor for RA, he asserts that the increased risk declines slowly back to normal within 10 years of smoking cessation. Because Petitioner quit smoking approximately 17 years before the onset of his disease, Petitioner contends that smoking is not a factor in his situation.

Petitioner cited Firestein & McInnes, *Immunopathogenesis of Rheumatoid Arthritis*, 46 IMMUNITY 183-96, 2017 (filed as Ex. 50) (hereinafter "Firestein & McInnes") in support of his position. The authors of this review article note that

> Epidemiologic/genetic studies, particularly those arising from impressive Swedish registries, have highlighted the role of cigarette smoking as a prominent environmental risk factor for RA[.] … The amount and duration of smoking are important, with the highest risk observed with greater than 20 pack-years of exposure. Risk declines slowly back to normal within 10 years of smoking cessation, suggesting that effects are not solely toxin dependent but may also arise by altering immunologic function.

Firestein & McInnes at 185. The authors cited to one study (Kallberg et al. 2011) as support for the point that risk declines back to normal within 10 years of smoking cessation. *Id.*

Dr. Matloubian opined that the fact that Petitioner quit smoking approximately 17 years before his RA diagnosis does not impact his assessment that smoking was still a risk factor in Petitioner's case. Third Matloubian Rep. at 3. Dr. Matloubian noted that since RA is thought to go through multiple pre-clinical phases years prior to clinical presentation, Petitioner's smoking would have led to a breakdown in tolerance resulting in autoimmunity. *Id*. Dr. Matloubian concluded "once this breakdown of tolerance has been triggered by smoking in a genetically susceptible person, it can continue to progress to full blown clinical RA even if that person quits smoking." *Id.*

Dr. Matloubian testified at the entitlement hearing that although Petitioner quit smoking 17 years before he developed RA, "the insult" of smoking had still taken place. Tr. at 250. In support of his position, Dr. Matloubian referred to the Liu article. The authors in Liu asked the question: "what's the impact of smoking cessation on developing RA in different serological phenotypes"? *Id.* They concluded that "With increasing duration of smoking cessation, a decreased trend was observed in risk for all RA." Liu at 1. However, the authors went on to note that "a modestly elevated RA risk was still detectable 30 years after quitting smoking." *Id.* Liu also discussed Kallberg, stating that "this case-control study may have been limited by recall bias and there were few cases in the sustained smoking cessation group so there may have been limited power to detect a true difference." *Id.* at 7.

Petitioner responded to this testimony by highlighting the fact that the study discussed by Liu involved 230,000 women and did not include men. Indeed, the authors in Liu noted that one

possible limitation of their study was that a study population "consisting of mostly healthy, well-educated, white US women working in nursing professions at baseline, may not be representative of the general population." Liu at 9. In response to Petitioner's point that the study only involved women, Dr. Matloubian noted that the findings in Liu also discussed "other studies that include men and women with similar findings." Tr. at 374.

Liu did refer to other studies, although I did not note any studies that included men. They referenced "[r]ecent results from the French E3N cohort study prospectively followed 71,248 women since 1990 and found that past smokers (HR 1.32, 95% CI 1.06–1.64) and current smokers (HR 1.57, 95% CI 1.13–2.19) had increased RA risk compared to never smokers." Liu at 7. The Liu article also referred to the Swedish Mammography Cohort study, which followed 34,101 women from 1997 to 2010, identifying 219 incident RA cases. Liu summarized the results of this study, noting that "[p]ast smokers who quit smoking ≥15 years had increased RA risk (HR 1.99, 95% CI 1.23–3.20) compared to never smokers, suggesting that residual elevated RA risk remained even after sustained cessation." *Id.*

In evaluating the experts' testimony and the various pieces of medical literature, I conclude there is preponderant evidence to suggest that the risk of smoking decreases in the years following smoking cessation, but that the risk does remain elevated above that of a non-smoker, even after 20+ years. The Liu study is substantially better powered than the other studies discussed by the experts, involving 230,000 women who were studied over decades. I have also considered the fact that the literature filed into the record only includes studies involving women. The fact that men were not studied in Liu does not, in my opinion, reduce the value of that study to something below preponderant evidence.

Because smoking is a demonstrated risk factor for RA, it is more likely that this played a role in the development of Petitioner's disease rather than his flu vaccine. *See Stone v. Sec'y of Health & Hum. Servs.*, 676 F.3d 1373, 1379-80 (Fed. Cir. 2012) (finding that special masters can consider other possible sources of injury in making a determination under *Althen* prong two).[8]

As noted previously, autoantibodies likely precede clinically apparent symptoms of RA by a period of years. This position, espoused persuasively by Dr. Matloubian, further diminishes Petitioner's ability to demonstrate that flu vaccine *did cause* RA in this particular case. For all these reasons, I conclude that Petitioner has not presented preponderant evidence in support of *Althen's* second prong.

E. *Althen* Prong Three

The timing prong contains two parts. First, a petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and second, he must demonstrate that the onset of the disease occurred in this period. *Shapiro,* 101 Fed. Cl. at 542-43 (2011).

[8] I note that while smoking has been persuasively identified as an environmental trigger for RA, Respondent has not contended that smoking is an alternate cause of Petitioner's disease. Although I have considered Petitioner's history of smoking in my analysis, even without this evidence, I would have found Petitioner's prong two showing to have been deficient for the reasons articulated in this decision.

1. The Onset of Petitioner's Clinically Apparent RA

Petitioner contends that the onset of his symptoms of RA began several days after his flu vaccine. I find there is preponderant evidence to support this contention. I based this assessment on the medical records filed in the case.

On January 16, 2014, Petitioner visited Shores Podiatry Associates and complained of bilateral plantar foot pain. Ex. 6 at 1. Plantar foot pain refers to pain in the arch of the foot. Tr. at 223. Petitioner reported increased activity before onset of his pain. Ex. 6 at 1. The subjective portion of this record indicates that: "Patient states he was having pain in the heel of his feet and when he was at a hockey game he was walking on the ball of his feet. This caused pain in the ball and ankle of his feet. The heel is feeling fine now." *Id.* Petitioner indicated his foot pain was in the "4/5 IMS[9] and left dorsal midfoot." *Id.*

Petitioner returned to the podiatrist on March 10, 2014 complaining of pain in both feet and ankles which Petitioner indicated had been ongoing for "several months." Ex. 6 at 3. He also noted "recurrent pain & swelling in the 4 space right foot." *Id.* Petitioner also has pain in both shoulders. *Id.*

On April 29, 2014, Dr. Timothy Brennan, a rheumatologist at the Shores Rheumatology, PC, examined Petitioner and opined on his condition. Ex. 3 at 101. Dr. Brennan wrote,

> In October of 2013, he recalls a day where his left heel was painful following which he developed significant pain and discomfort in both sets of metatarsal phalangeal joints. Over time, this progressed to involve both wrists, his metacarpal phalangeal joints, both elbows, and the left knee. He identifies mornings as his worst time but can't quantify the length of his stiffness…

Id.

Petitioner met with Dr. Viju Moses, MBBS at the University of Michigan Rheumatology Clinic on September 2, 2014. Ex. 3 at 6. During that visit, Dr. Moses notes Petitioner's history:

> His symptoms started in Oct[ober] 2014, [sic] a few days after a flu shot. He first noted pain in the top of both feet. It was worse in the morning, and he had morning stiffness of 3-4 hours…Since Mar[ch] 2014 he started getting pain in his hands, w rists [sic], L[eft] shoulder, R[ight] knee and L[eft] buttock>R[ight] buttock. Unsure about morning stiffness for these joints…Fluctuating fatigue, sometimes severe.

Id. While this last record is certainly the most specific, it is not inconsistent with the other medical records in this case. I find that bilateral foot pain constituted the onset of Petitioner's RA. This finding is consistent with Dr. Zizic's testimony. *See* Tr. at 72, 81 (Dr. Zizic indicating that Petitioner's first symptom of RA was the pain and swelling in his feet). I further find there is

[9] The 4/5 IMS is the space between the 4th and 5th metatarsal. Tr. at 233.

preponderant evidence that Petitioner's onset of bilateral foot pain began approximately three days after his flu vaccination.

2. There is not Preponderant Evidence that Three Days Post-Flu Vaccine is a Medically-Acceptable Timeframe for Onset of RA

I note there is not extensive evidence in the record discussing the appropriate onset interval of RA after flu vaccine. Dr Zizic opined that "the petitioner developed RA symptoms within days after the influenza vaccination, and developed full-blown polyarthritis that was believed to be rheumatoid arthritis by both rheumatologists. This is precisely the timeline that one would expect from a vaccine induced autoimmune response." First Zizic Rep. at 22. This opinion was not substantially developed in subsequent reports or at hearing. Dr. Zizic generally testified that onset of disease two to three days after flu vaccine was medically appropriate under a molecular mimicry theory due to the recall response Petitioner likely experienced after having a prior flu infection. Tr. at 81-82.

Petitioner pointed to case reports as support for Dr. Zizic's opinion. *See* Basra at 1 (noting one week after flu shot, patient developed "joint pain and aches in hands, wrists, and knees, which resolved within a few days and patient became asymptomatic." Patient then received H1N1 vaccine and developed symptoms of RA one week later). Ex. 33 (a case report describing symptoms of polyarthritis that began a few days following systemic reaction to tetanus-toxoid vaccine); and Ex. 34 (joint manifestations after vaccination began 9 to 27 after rubella vaccine). These case reports involving vaccines other than the vaccine in the present case[10] do not provide preponderant evidence that three days is a medically-appropriate window for RA to develop after flu vaccine. In addition, and importantly, Dr. Matloubian persuasively opined that RA does not develop in a matter of days after an inciting event but is "years in the making". Tr. at 247.

I agree with Chief Special Master Corcoran's discussion of this topic in *Monzon v. Sec'y of Health & Hum. Servs*, 2021 WL 2711289 (Fed. Cl. Spec. Mstr. June 2, 2021). He stated:

> Indeed, given what is known about RA (and in particular the fact that the presence of the antibodies closely associated with it often long precede onset of RA symptoms), it is highly unlikely a vaccine could *either* cause these autoantibodies to develop in a medically-reasonable timeframe, or spark an autoimmune process dependent upon them, such that a vaccine administered close in time to appearance of RA symptoms could be deemed causal.

Monzon at *19. Petitioner has not presented preponderant evidence that three days is a medically acceptable timeframe for the onset of RA after flu vaccine, and thus has not established the third *Althen* prong.

[10] Although Basra discussed a patient who received seasonal flu vaccine, her symptoms resolved within a few days. Examining Basra in the context of the entire report demonstrates the authors were discussing the H1N1 vaccine.

VI. Conclusion

Upon careful evaluation of all the evidence submitted in this matter, including the medical records, the testimony, as well as the experts' opinions and medical literature, I conclude that Petitioner has not shown by preponderant evidence that he is entitled to compensation under the Vaccine Act. **His petition is therefore DISMISSED. The clerk shall enter judgment accordingly.**[11]

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master

[11] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by each filing (either jointly or separately) a notice renouncing their right to seek review.