In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 17-923V

Filed: March 12, 2025

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AMY MEHL,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

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Michael McLaren, Esq., Black McLaren, et al., P.C., Memphis, TN, for petitioner.
Mitchell Jones, Esq., U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Roth, Special Master:

On July 10, 2017, Amy Mehl ("Ms. Mehl" or "petitioner") filed a petition under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 *et seq.*[2] ("Vaccine Act" or "the Program"). Petitioner alleged that the Tdap vaccination she received on September 12, 2016 resulted in the development of rheumatoid arthritis ("RA") and/or other neurologic and physical impairments and other injuries that were "caused-in-fact" by the vaccination, or in the alternative, the seasonal influenza ("flu") vaccine she received on September 28, 2016 resulted in the development of RA and/or other neurologic and physical impairments and injuries that were "caused-in-fact" or significantly aggravated by that vaccine. *See* Petition ("Pet.") at 1, ECF No. 1.

Petitioner's expert did not address the flu vaccine in his opinions. *See* Pet. Ex. 27; Pet. Ex. 58; Pet. Ex. 60; Pet. Ex. 80. During the prehearing conference held on February 1, 2022, petitioner

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

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2018).

clarified that her claim in this case was that the Tdap vaccination she received on September 12, 2016 accelerated the onset of her RA by 2.5 years. Therefore, the *Althen* prongs were to be applied as the legal standard rather than the *Loving* factors. *See* ECF No. 80; *Loving ex rel. Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (2009).

For the reasons set forth below, I find that petitioner has failed to demonstrate by preponderant evidence that the Tdap vaccination she received on September 12, 2016 accelerated the onset of her RA by 2.5 years.

I. Procedural History

The petition was filed on July 10, 2017 and assigned to then Special Master Millman.[3] ECF Nos. 1, 4. Petitioner's affidavit and medical records were filed on July 25, 2017 and over the months that followed. Petitioner's Exhibits ("Pet. Ex.") 1-21, ECF Nos. 5-6, 10-12, 14, 16-17, 19.

Respondent filed his Rule 4(c) Report on April 2, 2018, advising against compensation and requesting transcriptions of certain medical records. ECF No. 22. Petitioner filed the requested records shortly thereafter. Pet. Ex. 22-26, ECF Nos. 23-25, 29-30.

Petitioner filed the expert report of Dr. Eric Gershwin and supporting literature on December 7, 2018. Pet. Ex. 27-56, ECF Nos. 32-35. Settlement negotiations followed but were unsuccessful. Respondent filed the expert report of Dr. Mehrdad Matloubian and supporting literature on August 5, 2019. Respondent's Exhibits ("Resp. Ex.") A-B, ECF Nos. 48-49. Dr. Gershwin's responsive report and supplemental report were filed on August 28, 2019 and November 13, 2019, respectively. Pet. Ex. 58-69, ECF Nos. 50, 52. On February 18, 2020, a supplemental report from Dr. Matloubian and supporting literature were filed. Resp. Ex. C, ECF Nos. 54, 84-85.

Petitioner requested that an entitlement hearing be scheduled. ECF No. 55. A hearing was set for February 7 and 8, 2022. ECF No. 73. While awaiting hearing, the parties tried to resolve the matter but to no avail. ECF Nos. 63-64, 67-68, 70.

Prehearing submissions were filed. ECF Nos. 75, 78-79.

An entitlement hearing was held on February 7 and 8, 2022. ECF No. 66.

Following the hearing, petitioner filed additional evidence and a supplemental expert report from Dr. Gershwin. Pet. Ex. 77-83, ECF Nos. 81-82, 86, 90-91. Respondent filed a responsive expert report from Dr. Matloubian. Resp. Ex. D, ECF No. 93. The record was closed on June 6, 2022. ECF No. 94.

The matter is now ripe for an entitlement decision.

[3] This matter was reassigned to Special Master Horner on June 5, 2019 and then to the undersigned on September 16, 2021. ECF Nos. 45, 71-72.

II. Autoimmune Diseases and Rheumatoid Arthritis

Autoimmune diseases affect nearly 5% of the general population, but the causes are poorly understood. Pet. Ex. 29 at 1.[4] Genetic vulnerability is necessary but insufficient on its own to "to explain the loss of tolerance" in autoimmunity. Environmental factors play a role as well. Various mechanisms by which environmental factors can generate autoimmunity include molecular mimicry, self-antigen modification, bystander activation, and immune reactivity modulation. *Id*. In all instances, "the prolonged time between an environmental trigger and the appearance of autoreactivity and subsequent clinical disease" must be considered. *Id*.

Rheumatoid arthritis ("RA") is a systemic, inflammatory autoimmune disease largely of the joints with tenderness and swelling of the joints as the hallmark for clinical diagnosis. Resp. Ex. C Tab 1.[5] RA includes findings of synovitis,[6] systemic inflammation, and autoantibody production of rheumatoid factor ("RF")[7] and citrullinated peptide ("CCP").[8,9] Resp. Ex. A Tab 1;[10] Resp. Ex. A Tab 12.[11] While 50% of the risk for development of RA is attributed to genetic factors, smoking is the main environmental risk. Resp. Ex. A Tab 12 at 1. RA is most common in the elderly and in women. *Id*.

Approximately two-thirds of patients with RA test positive for RF and/or anti-CCP. Generally, autoantibody positivity increases closer in time to the onset of clinical (symptomatic) arthritis, but autoantibodies can exist in RA patients for up to 15 years before diagnosis. Pet. Ex. 70 at 3.[12] RA develops in phases/stages,[13] which include an "asymptomatic" phase of genetic risk; an asymptomatic phase of "immune activation" with abnormalities in autoantibodies seen up to 14 years prior to the development of clinical/symptomatic RA; an asymptomatic "pre-clinical" phase

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[4] Carlo Selmi et al., *The Long and Latent Road to Autoimmunity*, 15 CELLULAR & MOLECULAR IMMUNOLOGY 543 (2018), filed as "Pet. Ex. 29".

[5] Kevin D. Deane, MD, PhD & V. Michael Holers, MD, *The Natural History of Rheumatoid Arthritis*, 41 CLINICAL THERAPEUTICS 1256 (2019), filed as "Resp. Ex. C Tab 1".

[6] Synovitis is inflammation of a synovial membrane, which is the inner of the two layers of the articular capsule of a synovial joint, composed of loose connective tissue and having a free smooth surface that lines the joint cavity. Synovitis, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1826 (33rd ed. 2020) [hereinafter DORLAND'S]; Membrana synovialis capsulae articularis, DORLAND'S 1112.

[7] Rheumatoid factor is a marker of antibodies directed against antigenic determinants, i.e., Gm, in the Fc region of the IgG class of immunoglobulins; these are found in the serum of about 80 percent of persons with classical or definite rheumatoid arthritis but only about 20 percent of those with juvenile rheumatoid arthritis. Rheumatoid factors may be of the IgM, IgG, or IgA classes of immunoglobulins, although serologic tests measure only IgM. Rheumatoid factor, DORLAND'S 669.

[8] Citrullinated peptide is a synthetic, citrulline-containing peptide with a cyclic structure, used in assays for rheumatoid arthritis; the presence of antibodies to this peptide is highly specific for rheumatoid arthritis. Cyclic citrullinated peptide, DORLAND'S 1388.

[9] The literature uses both "ACPA" the more current acronym and "anti-CCP" to refer to anti-citrullinated protein antibodies. The experts used "anti-CCP," therefore "anti-CCP" will be used in this Decision for consistency and to avoid confusion.

[10] Iain B. McInnes, F.R.C.P., Ph.D. & Georg Schett, M.D., *The Pathogenesis of Rheumatoid Arthritis*, 365 N. ENG. J. MED. 2205 (2011), filed as "Resp. Ex. A Tab 1".

[11] David L. Scott et al., *Rheumatoid Arthritis*, 376 LANCET 1094 (2010), filed as "Resp. Ex. A Tab 12".

[12] Laurette van Boheemen & Dirkjan van Schaardenburg, *Predicting Rheumatoid Arthritis in At-Risk Individuals*, 41 CLINICAL THERAPEUTICS 1286 (2019), filed as "Pet. Ex. 61" and "Pet. Ex. 70".

[13] Some literature includes 4 phases, while other literature discusses the latent period as 6 phases. *See* Resp. Ex. A Tab 11.

with abnormal biomarkers of inflammation and arthralgias; and the final phase of clinically apparent RA with pain, stiffness, swelling, and synovitis on examination. Pet. Ex. 74 at 2.[14]

More specifically, the preclinical phase of RA is characterized by the appearance of anti-CCP followed by positive RF. Over time, anti-CCP increases with a more pro-inflammatory profile. Elevations of cytokines, chemokines, and acute phase reactants are present for 2-12 years before RA diagnosis, with increasing levels of cytokines and chemokines thought to correspond with the decreasing time to diagnosis. Pet. Ex. 75 at 4;[15] Resp. Ex. C Tab 1 at 5.[16] The consequences of this inflammatory cascade are synovial inflammation and associated damage to articular cartilage and bone. Resp. Ex. A Tab 12 at 1.[17] Key to this inflammation cascade is the overproduction of tumor necrosis factor ("TNF") which has many causes including interactions between T and B lymphocytes, synovial-like fibroblasts, and macrophages, which lead to the overproduction of cytokines such as interleukin-6 ("IL-6"), which in turn drives persistent inflammation and joint destruction. *Id*.

Hepatitis B virus, parvovirus B19, rubella infection or vaccination, and Epstein Barr virus ("EBV") have been noted to produce polyarthritis that mimics early RA but is self-limited and resolves in 2-4 weeks. Resp. Ex. A Tab 3 at 1.[18] For RA, it is unlikely that "a single pathogenetic mechanism could explain the occurrence of arthritis after a natural virus infection and after administration of an inactivated toxoid." Pet. Ex. 71 at 2.[19] More likely, multiple agents are capable of triggering the immunological process that manifests as clinical RA. Pet. Ex. 71 at 1; Pet. Ex. 74 at 1;[20] Resp. Ex. A Tab 6 at 1.[21]

Recently the focus in the pathogenesis of RA has been on diseases of oral tissue, lung, and gut with a hypothesis that mucosal tissue surfaces and microbes (bacteria) play a role. Pet. Ex. 70 at 3.[22]

The criteria for classification of RA as set forth by the American College of Rheumatology ("ACR") and the European League Against Rheumatism ("EULAR") includes: 1) number and site of involved joints with synovitis (not just pain); 2) serological abnormalities (low vs. high RF or anti-CCP antibody titers); 3) elevated acute phase reactants (ESR and CRP) at the time the physician observes joint swelling; and 4) duration of symptoms (more than six weeks). The highest

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[14] Elizabeth W. Karlson, MD & Kevin Deane, MD, PhD, *Environmental and Gene-Environment Interactions and Risk of Rheumatoid Arthritis*, 38 RHEUMATIC DISEASE CLINICS OF NORTH AMERICA 405 (2012), filed as "Pet. Ex. 66" and "Pet. Ex. 74".

[15] Elizabeth W. Karlson et al., *RA: From Risk Factors and Pathogenesis to Prevention*, 55 RHEUMATOLOGY 6 (2016), filed as "Pet. Ex. 67" and "Pet. Ex. 75".

[16] Deane & Holers, *supra* note 5.

[17] Scott et al., *supra* note 11.

[18] John B. Imboden, MD et al., *Rheumatoid Arthritis*, *in* Current Diagnosis & Treatment: Rheumatology (McGraw-Hill Education 3rd ed., 2013), filed as "Resp. Ex. A Tab 3".

[19] Chakravarty Symmons, *Can Immunisation Trigger Rheumatoid Arthritis?*, 52 ANNALS OF THE RHEUMATIC DISEASES 843 (1993), filed as "Pet. Ex. 62", "Pet. Ex. 71", and "Resp. Ex. A Tab 19".

[20] Karlson & Deane, *supra* note 14.

[21] Laura Hunt & Paul Emery, *Defining Populations at Risk of Rheumatoid Arthritis: The First Steps to Prevention*, 10 NATURE REVIEWS RHEUMATOLOGY 521 (2014), filed as "Resp. Ex. A Tab 6".

[22] van Boheemen & van Schaardenburg, *supra* note 12.

score is given to involvement of >10 small joints (5 points), whereas involvement of 2-10 large joints yields only 1 point. Resp. Ex. A at 6.

III. Factual Record

A. Medical History Pre-Vaccination

Petitioner's medical history is complicated by migraines, hypertension, IBS, excoriated lichen planus,[23] intractable cervical, hip, and lower back pain with surgical interventions, intra-articular facet injections, and the need for ongoing pain management and medications, among other conditions. She also suffers from chronic Epstein Barr Virus[24] with active flares. Pet. Ex. 2 at 101, 104, 181-82, 232, 291, 355, 490, 567, 620; Pet. Ex. 4 at 2-3; Pet. Ex. 7 at 9-10; *see generally* Pet. Ex. 8; Pet. Ex. 10; Pet. Ex. 24. Petitioner required counseling to cope with living in chronic pain. Pet. Ex. 4 at 187.

In 2013, petitioner's blood work showed elevated Erythrocyte Sedimentation Rate ("ESR")[25] of 32 and cortisol levels.[26] Pet. Ex. 24 at 2. She reported an episode of jerking of her arm, legs, chest, and mouth with tingling and sharp pain in her head. *Id*. at 3; Pet. Ex. 7 at 9. A history of migraines was noted. Pet. Ex. 7 at 10.

In 2014, petitioner complained of continuous fatigue. She tested positive for EBV on July 1, 2014 and was out of work; she continued to test positive for EBV until October 13, 2014. Pet. Ex. 24 at 5-7. In late 2014, her pain management physician documented complaints of joint pain and stiffness in addition to her ongoing back pain and muscle spasms. Pet. Ex. 4 at 163-68.

On October 21, 2014, petitioner presented to her primary care physician ("PCP") with complaints of extensive fatigue, stiffness in her joints, body aches, forgetfulness, difficulty sleeping at night, falling asleep during the day, changes in bowel habits, craving for salt and sugar, weekly migraines, weight loss, and no energy. The impression included joint pain and fatigue. She received a Fluzone vaccine at that visit and was referred to a rheumatologist, Dr. Efros. Pet. Ex. 24 at 7.

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[23] Lichen planus is an inflammatory, pruritic disease of the skin or sometimes oral mucosa, genital mucosa, or nails; it may be acute and widespread or chronic and localized. Lichen planus, DORLAND'S 1019-20.

[24] Epstein Barr Virus, human herpesvirus 4, is a virus of the genus *Lymphocryptovirus* that causes infectious mononucleosis. Human herpesvirus 4, DORLAND'S 843, 2030. Chronic EBV is also called chronic fatigue syndrome, which is defined as persistent debilitating fatigue lasting longer than 6 months, with other known medical conditions having been ruled out by clinical diagnosis, accompanied by at least four of the following: significantly impaired short-term memory or concentration, muscle weakness, pain in multiple joints without swelling or redness, sore throat, tender lymph nodes, headaches, unrefreshing sleep, and malaise that lasts more than 24 hours following exertion. Chronic fatigue syndrome, DORLAND'S 1795.

[25] Erythrocyte Sedimentation Rate is the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood, measured by the distance the top of the column of erythrocytes falls in a given time interval under specified conditions; an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins, which decrease the zeta potential on erythrocytes by dielectric shielding and thus promote rouleau formation. Erythrocyte Sedimentation Rate, DORLAND'S 1569.

[26] Cortisol is the major natural glucocorticoid synthesized in the zona fasciculata of the adrenal cortex; it affects the metabolism of glucose, protein, and fats and has appreciable mineralocorticoid activity. It also regulates the immune system. Cortisol, DORLAND'S 417.

Petitioner presented to Dr. Efros on October 28, 2014. Pet. Ex. 23 at 1.[27] She reported a history of serious injuries in a car accident in 2003 which had required pain management and medications since. In June of 2012, she suffered from increased fatigue, leg weakness, and dizziness and was diagnosed with Epstein Barr Virus which resulted in her being out of work until September of 2012, but she continued to suffer from fatigue. She had increased Prolactin[28] level and a cyst on the pituitary gland seen on MRI in March 2013. She suffered a relapse of EBV in June of 2014, but she still had fatigue, muscle achiness, weakness, and weight loss. *Id*. Blood work on that date was anti-CCP positive with negative RF. Pet. Ex. 2 at 339. Dr. Efros requested her records and a follow up visit. Pet. Ex. 23 at 1. She did not return. She was out of work again between December 2014 and March of 2015 following a hysterectomy Pet. Ex. 24 at 8-9.

Throughout 2015, petitioner complained of joint and muscle pain and stiffness, as well as muscle swelling and chronic back pain. Pet. Ex. 4 at 98, 105, 118, 124, 130, 136, 142, 168.

She was diagnosed with strep and prescribed amoxicillin followed by Augmentin in March of 2015. Pet. Ex. 24 at 9-10. She developed mouth ulcerations in April of 2015. *Id*. at 10; Pet. Ex. 11 at 1-2; Pet. Ex. 12. Biopsy confirmed excoriated lichen planus.[29] Throat cultures were also positive for yeast Chlamydia[30] through August of 2015. Pet. Ex. 24 at 11.

She received a flu vaccine on September 9, 2015. Pet. Ex. 24 at 11. She was prescribed Augmentin then Omnicef for bronchitis in December of 2015. *Id*. at 12.

Throughout 2016, petitioner complained of joint pain and stiffness, muscle stiffness, and chronic back and neck pain when she presented to pain management. Pet. Ex. 4 at 53, 70, 84, 91. The pain management records document routine toxicology monitoring. Her prescriptions included Amitriptyline,[31] Topamax,[32] Skelaxin,[33] Fentanyl patches,[34] and Tramadol.[35] *See generally id*.

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[27] Exhibit 23 is a transcription of Exhibit 5 and is being used for references.

[28] Prolactin is an anterior pituitary hormone with 198 amino acids, molecular weight 23,000, which stimulates and sustains lactation in postpartum mammals after the mammary glands have been prepared by other hormones such as estrogens, progesterone, growth hormone, corticosteroids, and insulin. It also plays essential roles in the maintenance of immune system functions. Prolactin, DORLAND'S 1501.

[29] This record states that she was seen at Rutgers and that biopsy confirmed the diagnosis; however, neither the records from Rutgers nor the biopsy could be located within the records filed.

[30] Chlamydia is a genus of bacteria of the family Chlamydiaceae, consisting of gram-negative, glycogen-producing, coccoid organisms that multiply only within a host cell and have a unique growth cycle. They are common pathogens. Chlamydia, DORLAND'S 339.

[31] Amitriptyline hydrochloride is a tricyclic antidepressant of the dibenzocycloheptadiene group, also having sedative effects; it is also used in the treatment of enuresis, chronic pain, peptic ulcer, and bulimia nervosa. Amitriptyline hydrochloride, DORLAND'S 63.

[32] Topamax is the trademark for a preparation of topiramate, which is a substituted monosaccharide used as an anticonvulsant in the treatment of partial seizures. Topamax, DORLAND'S 1910; Topiramate, DORLAND'S 1910.

[33] Skelaxin is the trademark for a preparation of metaxalone a centrally acting skeletal muscle relaxant used in the treatment of painful musculoskeletal conditions. Skelaxin, DORLAND'S 1694; Metaxalone, DORLAND'S 1129.

[34] Fentanyl citrate is an opioid analgesic that interacts predominantly with opioid μ-receptors and is used mainly preoperatively, postoperatively, and during surgery but also to relieve chronic severe pain. Fentanyl citrate, DORLAND'S 681.

[35] Tramadol hydrochloride is an opioid analgesic used for the treatment of moderate to moderately severe pain. Tramadol hydrochloride, DORLAND'S 1920.

Petitioner had an MRI on January 20, 2016 for increased neck and back pain with numbness and tingling for which she used Fentanyl patches. Pet. Ex. 24 at 12. The MRI showed mild degenerative changes in the facets and uncovertebral joints. Pet. Ex. 3 at 24-25. She had elevated triglycerides and vitamin D deficiency. *Id*. at 51-52. In March of 2016, she reported a flare of lichen planus due to family stress. Pet. Ex. 4 at 74.

On September 12, 2016, petitioner presented to Atlantic Health after cutting her thumb the morning before. She reported a history of autoimmune disease (oral lichen planus), chronic back pain, and not having had a tetanus shot in more than 10 years. She reported a history of swelling from tetanus vaccines. The pros and cons of a Tdap were discussed, and the Tdap vaccine was administered in her left deltoid. Pet. Ex. 2 at 94-99.

B. Medical History Post-Vaccination

Four days later, on September 16, 2016, petitioner presented to her PCP reporting fever over past 3 days and joint pain including in her thumb. No joint swelling was noted on examination and there was full range of motion of her thumb with minimal swelling over the left thumb area. The impression was possible tetanus reaction and thumb laceration with infection and pain. She was prescribed 10 days of Augmentin. Pet. Ex. 24 at 13.[36] Blood work was "within normal limits" except for elevated ESR, C-reactive protein ("CRP"), and Rheumatoid Factor. Her RF was at 38 on a reference range of 0-15 IU/ml. The plan was to repeat blood work after completing Augmentin. *Id*.; Pet. Ex. 3 at 43, 46.

Petitioner presented to pain management on September 28, 2016. She reported cutting her left thumb, developing "serum sickness after the [Tdap] injection" with "profound body pain" and elevated inflammatory markers. She was going to her primary later that day to see if this had resolved. Pet. Ex. 4 at 43. "She is feeling much better but the month was difficult." *Id*. Review of systems showed no joint swelling, pain, or stiffness that day. *Id*. at 46.

Petitioner reported that she had slight joint pain and fatigue at her PCP visit later that day. No joint swelling was noted on examination. She received a flu vaccine. Pet. Ex. 24 at 13. Repeat blood work performed two days later was within normal limits for ESR and CRP. RF had decreased to 24 and was noted to be "almost within normal limits." Pet. Ex. 3 at 40-42.

There were no medical records or communications filed until approximately six weeks later, on November 9, 2016, when petitioner presented to her PCP reporting "[j]oint pain which has increased, swelling occurred in joints . . . Some swelling of hands and ankles." Pet. Ex. 24 at 13. "[N]o swelling of joints" was noted on examination. The impression was joint pain and fatigue. The plan included blood work, prednisone taper for 9 days, and rheumatology. *Id*. Blood work was noted to be "within normal limits. Much improved . . . Rheumatoid Factor still at 24." *Id*. at 13-14.

Petitioner's next medical visit was on December 7, 2016. She reported a difficult month with medical issues, "profound swelling of her joints" and a "second episode" of "serum sickness

[36] Exhibit 24 is a transcription of Exhibit 3 and is being used for references.

since her tetanus injection." She had been prescribed a steroid taper that helped. Review of systems was positive for back pain, joint pain, joint swelling, joint stiffness, muscle pain, muscle swelling, and muscle stiffness. Pet. Ex. 4 at 36, 39.

Petitioner presented to Dr. Efros on December 29, 2016. She reported her history since her last visit two years before which included a hysterectomy after which she was less tired, but then entered menopause, a diagnosis of erosive lichen planus and secondary burning mouth syndrome with flares treated with an oral steroid rinse, receipt of a tetanus shot on September 12, 2016 with "immediate generalized achiness followed by swelling of her left thumb, DIP and left second and third anterior MCP's,"[37] and elevated ESR, CRP and RF on September 16, 2016. Pet. Ex. 23 at 2. She reported that she improved then received a flu shot on September 28[38] and had swollen lymph nodes and a temperature of 103 twice. Repeat blood work on September 30, 2016 two days after the flu vaccine showed normal ESR and CRP and her RF had gone down to 24. She reported that she was then okay until November when "the same thing happened with her left thumb and left foot." She was prescribed a prednisone taper with immediate improvement. November blood work showed normal ESR and CRP and her RF was at 24. She reported being okay again until 12 days ago when she had a URI and developed "the same symptoms in her left thumb and left foot." She denied any new musculoskeletal symptoms. She was under the care of pain management with prescribed medications. *Id*. Physical examination revealed left first DIP swelling and tenderness and left second MTP (anterior) tenderness to palpation. A prednisone taper was prescribed. Dr. Efros wrote that he had a "[v]ery long discussion with patient about possible diagnoses and treatment options. RA? Relationship between tetanus shot and initiation of symptoms".[39] *Id*. Blood work on that date showed RF at 85, positive anti-CCP, and normal ESR and CRP. *Id*. at 3.

In a phone call with Dr. Efros on January 3, 2017, petitioner reported nausea and vomiting from prednisone, but her swelling had gone down. She still had discomfort in her left thumb, left toe, and slightly in her left index finger. Prednisone was reduced. Pet. Ex. 23 at 3.

On January 4, 2017, petitioner presented to pain management reporting swelling and pain in her left thumb and foot and that Dr. Efros believed it was "brought on by the serum toxicity" from a tetanus injection. If it were to resolve on its own, it would do so within the next two months or by the six-month mark. She was on a third steroid taper which helped somewhat, but she tolerated steroids poorly. Pet. Ex. 4 at 29.

Petitioner spoke to Dr. Efros on January 13 and January 18, 2017 after finishing the prednisone to report that she had left thumb and foot swelling and right third finger swelling as well. Zorvolex was prescribed for inflammation. Pet. Ex. 23 at 3.

At a visit with Dr. Efros on January 25, 2017, petitioner reported that the Zorvolex helped in some ways, but she had new issues, including "(1) left foot is so-so with numbness in second

[37] This is not documented in any record filed in this case. DIP refers to Distal Interphalangeal Joint and MCP refers to Metacarpophalangeal Joint, both of which are terms used to describe symptoms of RA.

[38] Although the record states she received the flu vaccine on September 29, the contemporaneous record shows the flu vaccine was administered on September 28. Pet. Ex. 24 at 13.

[39] The record did not contain any details regarding the content of this conversation or what Dr. Efros meant by "Relationship between tetanus shot and initiation of symptoms".

and third toes and 'ball on the top' not as bad as previously. (2) left thumb has no major swelling. (3) new areas are right third PIP swelling and more recently right second DIP issues. (4) left medial wrist discomfort with swelling. (5) right ankle pain at night. Getting frustrated. Other meds remain unchanged." Pet. Ex. 23 at 3. Physical examination revealed "left second MTP (anterior) tender to palpation with ? nodule . . . left thumb-MCP and IP slight swelling . . . right third PIP swelling/tend/erythema . . . right second DIP swelling/tend/erythema." *Id*. Dr. Efros noted a long discussion with petitioner about diagnoses and treatment, including "?early RA. ? reaction to DPT". *Id*. He prescribed prednisone in addition to Zorvolex. *Id*.

At a visit with a neurologist for her migraines on January 25, 2017, the record includes that "[s]he is dealing with the possibility of rheumatoid arthritis after undergoing various vaccinations." Pet. Ex. 7 at 25.

Petitioner called Dr. Efros on January 31, 2017 for sudden onset of pain and swelling of the tendon in her wrist. Prednisone was increased. Pet. Ex. 23 at 3. Petitioner did not return to Dr. Efros.

At her February 1, 2017 pain management visit, petitioner reported that a few days before, she had a flare of her inflammatory disorder and developed severe tendonitis of the left wrist. She was prescribed prednisone which helped. She was using the Fentanyl patch and her lower back pain improved with steroid usage. Pet. Ex. 4 at 22. On examination, she was positive for back pain, joint stiffness, and joint swelling. *Id*. at 25.

Petitioner sought a second opinion from rheumatologist, Dr. Bartov, on February 8, 2017. Pet. Ex. 2 at 545. She reported a history of cutting her thumb slicing a bagel in September of 2016, receiving a tetanus shot the next day, developing joint and muscle pain throughout her body within 24 hours, receiving a flu shot two weeks later with flu-like reaction and intermittent swelling of her left thumb and left foot, seeing her PCP, and being prescribed a prednisone taper which resolved the joint swelling and pain. *Id*. In December she had a URI and her right hand, left foot, and left thumb started to swell. She had little improvement with prednisone and NSAIDs prescribed by Dr. Efros. *Id*. She had chronic back pain from a previous injury and migraines and used Fentanyl patches. *Id*. She smoked electronic cigarettes but did not drink but was a former smoker. There was possible RA in her grandmother. *Id*. at 546-47. Examination revealed, "[p]ain with palpation of left wrist, right 3rd PIP joint of hand, and left 3rd MCP joint of foot. No synovitis. Grip is 100%. No rheumatoid nodules, interosseous wasting, swan necks or boutonniere's." *Id*. at 548. The impression/plan was "[s]uspected early RA given synovitis, positive RF and elevated acute phase reactants, possibly triggered by tetanus vaccine" *Id*. She was encouraged to stop smoking and instructed to continue current pain regimen for her chronic back pain. *Id*.

Petitioner returned to Dr. Bartov on February 15, 2017. She reported increasing prednisone over the weekend to 35 mg a day due to ongoing synovitis but was back to 5 mg. Her lab results were notable for low vitamin D and "weak positive CCP." Pet. Ex. 2 at 574. She also had a positive TB test. Pet. Ex. 16 at 36. On examination, she had tenderness and swelling of the right and left hands at the 2nd PIP, 3rd PIP, and 4th PIP, as well as tender and swollen joint count of 6. Pet. Ex. 2 at 576. The impression was CCP positive, non-erosive RA and low vitamin D. She was to start

Methotrexate, continue prednisone and start folic acid. She was again encouraged to stop smoking and told to continue with her treatment plan of lower back pain. *Id*. at 582.

Petitioner returned to Dr. Bartov on March 1, 2017 and March 17, 2017. She was doing well on Methotrexate and prednisone and had cut back on smoking, but still had morning stiffness for about ten minutes with pain in her wrist and hand. Pet. Ex. 2 at 599; Pet. Ex. 6 at 24, 35; *see also* Pet. Ex. 16. Blood work was positive for anti-CCP antibody and RF. Pet. Ex. 6 at 33, 41. ANA was negative. Pet. Ex. 16 at 4.

At her March 31, 2017 visit, Dr. Bartov noted improvement of pain and swelling with prednisone 5mg daily and Methotrexate 20mg weekly. She still complained of a few minutes of morning stiffness. She was still smoking e-cigarettes. Pet. Ex. 16 at 40. Dr. Bartov's impression was seropositive, anti-CCP positive, non-erosive RA with low activity. She was to continue Methotrexate 20mg weekly, taper off prednisone, stop smoking, continue chronic pain medication regimen, and take high doses of vitamin D. *Id*. at 51.

Petitioner presented to Dr. Bartov on April 20, 2017 and reported that her RA felt best on 5mg of prednisone but it had too many side effects. She was still using e-cigarettes but trying to cut down. Pet. Ex. 16 at 86. Dr. Bartov's impression was the same. Methotrexate 20mg weekly was continued, with prednisone reduced to 2.5 mg daily. Humira was discussed, she was to stop smoking, continue with chronic pain medication regimen, and high dose vitamin D. *Id*. at 92.

By June 29, 2017, petitioner had completed 4 Humira injections with no side effects and 75% improvement. She still had bilateral hand and left foot pain and some morning stiffness. Pet. Ex. 16 at 132. She had quit smoking. Her leukopenia[40] was being monitored. *Id*. at 136.

Petitioner suffered from active EBV infection again in July of 2017. She was taking Humira, and her RF was at 231, but she had low disease activity. Pet. Ex. 16 at 151, 158. She was ANA positive which Dr. Bartov thought was likely due to EBV rather than active RA given her ESR/CRP were normal. *Id*. at 158, 161-62. She was doing well but for pain between the 2nd and 3rd toes on her left foot. *Id*.

An MRI of her foot in August of 2017 showed bursitis with possible neuroma. Pet. Ex. 17 at 7-9. Dr. Bartov did not believe her bursitis and neuroma were related to her RA. Pet. Ex. 16 at 183.

At her August 16, 2017 visit with pain management, petitioner reported active EBV, a neuroma in her left foot, bad RA, a change to Humira, and aggravation of her back pain. Pet. Ex. 14 at 1-9. An MRI of her back was ordered. Her foot issues were attributed to her history of herniated discs. Pet. Ex. 13 at 6; *See* Pet. Ex. 20.

Petitioner returned to Dr. Bartov on August 17, 2017, and reported pain behind her knees, swollen hands, and a neuroma in her foot. Blood work revealed acute EBV infection, ANA 1:320,

[40] Leukopenia is the reduction in the number of leukocytes in the blood below about 5000 per mm^3. Leukopenia, DORLAND'S 1016.

RF of 231 and normal CRP. Pet. Ex. 16 at 195. Dr. Bartov's impression was high activity of RA and Remicade was prescribed with prednisone. *Id*. at 199.

A request form for a consult dated October 10, 2017 was filed. It is unclear who filled out the form or who added notes in the margin of the form.[41] Pet. Ex. 18 at 1-5. The form includes a history of present illness "tetanus vaccine last year", "c/o aches/pains, PCP did [blood work] – inflammatory was high, 2 [weeks]", "[diagnosed] – serum sickness", "later got flu vaccine – 103 temp x 3 days + enlarged lymph node", "Nov 2016 = where cut thumb = swelling = then moved to another finger", "Dec = hand swelling + joint swelling. Saw Dr. Efros . . . – felt it was from vaccine (Tetanus)". Dr. Bartov diagnosed RA in February 2017. *Id*. at 1. For vaccination status/reactions the form includes "large welt" with her original tetanus vaccine, and elevated temperature and enlarged lymph nodes with flu vaccine. *Id*. at 2. The end of the form includes a diagnosis of "autoimmune response vs. serum sickness vs. vaccine hypersensitivity" in the same handwriting as the notes in the margin. *Id*. at 6.

Petitioner presented for occupational therapy ("OT") for her hand in November of 2017 and reported a history of painful swelling in her left hand the day after a tetanus shot in September of 2016, followed by whole body achiness with both hands swollen and painful which then traveled to her left foot. She saw Dr. Efros then Dr. Bartov. She received infusions every other month for RA and is recovering from active EBV that started in May of 2017. She was not working and received disability. She previously worked at an animal clinic part-time. She has leukopenia, vitamin D deficiency, and RA. Pet. Ex. 21 at 8. OT was recommended twice per week for six weeks, but petitioner attended two visits then reported that her PCP wanted her to discontinue OT due to increased pain and swelling. *See generally id*.

Petitioner underwent surgical excision of the foot neuroma in August of 2018. *See generally* Pet. Ex. 25.

Petitioner's updated medical records include treatment with Dr. Bartov for RA and more recently diagnosed fibromyalgia. According to Dr. Bartov, petitioner is able to perform all activities of daily living and has minimal joint pain or swelling. Pet. Ex. 79 at 4, 7.

C. Petitioner's Affidavit

Petitioner's affidavit dated July 1, 2017 contains direct quotes from her medical records. *See generally* Pet. Ex. 1.

Petitioner affirmed the following: She received a Tdap vaccination on September 12, 2016 after cutting her finger with swelling from the vaccine in the past. Pet. Ex. 1 at 1. Within 24 hours of her receipt of the Tdap vaccination, she had joint and muscle pain throughout her body and swelling of her thumb. *Id*. She saw her PCP on September 16, who considered a possible tetanus shot reaction and ordered blood work. She had elevated ESR, CRP, and RF. *Id*. at 2. She returned to the PCP on September 28, 2016 for her flu shot. She also presented to pain management that

[41] The record is designated on the docket as belonging to Dr. Weinreb. The form is handwritten and is largely illegible.

day and reported that she "'developed serum sickness with profound body pain after [her] recent tetanus injection,"' and had elevated RF. *Id*. She returned to the PCP on November 9, 2016 for ongoing fatigue, joint pain, and joint swelling. RF was still elevated. Prednisone was prescribed. *Id*.

Petitioner affirmed that she presented to Dr. Efros on December 29, 2016 for continuing complaints. Dr. Efros considered RA, questioned the relationship between the Tdap and her symptoms, and prescribed high dose prednisone with a taper. Her RF was still elevated. Pet. Ex. 1 at 2-3. She returned to Dr. Efros on January 25, 2017 for ongoing symptoms and was diagnosed with RA "as a possible reaction to the tetanus vaccination." *Id*. at 3.

Petitioner quoted from her record from a visit with a neurologist on January 25, 2017, that she was "'dealing with the possibility of [RA] after undergoing various vaccinations.'" Pet. Ex. 1 at 3.

Petitioner affirmed that she went to Dr. Bartov on February 8, 2017 for a second opinion and provided a history of "joint and muscle pain throughout [her] body following [a] September 2016 tetanus shot with symptoms continuing to present after [her] flu shot that same month." Dr. Bartov "'[s]uspected early RA given synovitis, positive RF and elevated acute phase reactants, possibly triggered by tetanus vaccination.'" Pet. Ex. 1 at 3. She still sees Dr. Bartov for active RA. *Id*.

Petitioner quoted from her pain management record that she had "'[s]erum sickness resulting in profound swelling of [her] joints following a tetanus injection in the summer of 2016."' Pet. Ex. 1 at 3-4.

Petitioner affirmed that she continues to suffer from RA symptoms and takes various medications. Pet. Ex. 1 at 4.

D. Petitioner's Testimony

Petitioner testified that she went out on disability in August of 2017 and now receives social security disability. Tr. 7-11.

Petitioner stated that her claim involves the tetanus shot she received on September 12, 2016 after cutting her finger on September 11. Tr. 11-14. She had local reactions from tetanus shots in the past but followed the doctor's instructions. Tr. 14, 22.

At the time she received the Tdap vaccine, she was an active mom with two children, a busy life, a physical job and no serious illnesses. Tr. 14, 17. She suffered a back injury from a car accident in 2003 while 8 months pregnant. Tr. 14-15. Her back pain got worse over time, and she received pain injections then fentanyl patches. Tr. 15. Her back pain is distinguishable from her joint and knee pain caused by the vaccine. Tr. 16.

Petitioner stated that since her receipt of the Tdap vaccine, she has aches and pain all over her body, does not go out, has groceries delivered, and spends most of her time lying down. She

had swelling of her left thumb the day after the vaccine which lasted into the next month when it went into her foot then into her other thumb. She reported joint pain to her PCP four days after the vaccine, but he did not find any evidence of joint swelling on examination. Tr. 17-20, 44-45.

Petitioner stated that she smoked as a teen, quit in her 20s, vaped for a while, quit smoking in 2012 but has vaped since. Tr. 20-21.

Petitioner stated that when she complained to her husband about her symptoms and pain after the vaccine, he wanted her to go to Dr. Efros who was his PCP. Tr. 22. She went to her own PCP who said it was probably a vaccine reaction. Petitioner stated that her finger was not infected but she was prescribed an antibiotic prophylactically. Tr. 24. She agreed that her medical record documented no joint swelling at that time. Tr. 45. She stated she then called the PCP a few days later when things did not get better, and he referred her to Dr. Efros. Tr. 25. She stated that her pain management doctor believed her complaints were a vaccine reaction and did not understand why it was going on for so long. Tr. 26. According to petitioner, her PCP called it "serum sickness," which means a vaccine reaction. Tr. 26-27. Petitioner recalled seeing Dr. Efros once, before the vaccine, but she could not remember why. Tr. 27-29.

Petitioner stated when she presented to Dr. Efros in December of 2016, she told him that she ached all over, had a lot of pain, and was limping. He thought it was a vaccine reaction. Tr. 30. He prescribed steroids because her foot was "really bad". Tr. 31. She went to Dr. Bartov for a second opinion. Tr. 31-32. Dr. Bartov reviewed her lab results, told her she had RA with an active flare and questioned why she was not on medication. She was prescribed "gateway" medications which did not work. Tr. 32. Dr. Bartov told her the vaccine could have started her RA. Tr. 32.

Petitioner continues to see her PCP, pain management, and Dr. Bartov. She saw a neurologist for migraines unrelated to her RA. Tr. 33-35. She saw someone for her foot pain but did not want surgery, so she didn't go back. Tr. 35-36. She gets infusions for her RA every two months which keeps her RA "at bay" so she doesn't have flares. Tr. 36, 38. She has received different medications by infusion over the years. The current one takes about an hour for the infusion, some others took up to six hours. Tr. 49-50.

Petitioner stated she currently suffers from high blood pressure, high cholesterol, back problems, migraines, fibromyalgia, and chronic fatigue syndrome. The fibromyalgia and chronic fatigue syndrome were diagnosed in 2018 and 2019 by Dr. Bartov and are all part of her vaccine injury according to Dr. Bartov. Tr. 41.

On cross examination, petitioner agreed that there was no evidence of joint swelling 4 days after the Tdap vaccination, 12 days after the Tdap vaccination, or on November 9, 2016—58 days after the Tdap vaccination. Tr. 45. She agreed that the first time joint swelling was noted by a physician on examination was December 29, 2016—roughly four months after vaccination—when she presented to Dr. Efros. Tr. 45-46. She also recalled seeing Dr. Efros in 2014 for pain, weakness, and weight loss. Tr. 46.

On redirect, petitioner stated that she had brain fog from fibromyalgia, was taking a lot of medication, loses words midsentence and does not remember things correctly. These symptoms

have worsened over the past few years, and she apologized for making mistakes during her testimony. Tr. 48-49. I asked her if she was saying that her ability to remember and testify accurately was affected. She responded, "yes". Tr. 50-51. Her attorney however, stated that it was his "understanding [] that she made a mistake as to which thumb she cut, and she was clarifying which thumb. I think that's as far as the misremembering or not remembering went in my mind." Tr. 51.

I then asked petitioner some questions. She responded as follows: She did not recall ever having joint pain and muscle weakness before the September 2016 Tdap vaccination. She had generalized weakness twice but from EBV (mono) which was from exhaustion not joint pain or weakness. Tr. 52. She did not recall seeing Dr. Efros in 2014 until asked about it during the hearing. She did not recall complaining to her PCP in 2012 or 2014 about joint pain and muscles aches prompting the referral to Dr. Efros. Tr. 52. Independent of her attorney's questions today, she did not have any specific recollection of seeing Dr. Efros in 2014 then stated that 2012 was a rough year, her son was sick, she lost a lot of weight and had mono, and did not remember much about why she went to Dr. Efros. Tr. 53. She did not recall any of the blood test results conducted by Dr. Efros in 2014. She did not recall anyone discussing RA until Dr. Bartov told her she had RA in 2017 and the Tdap vaccine was the possible cause. Tr. 53. She was diagnosed with fibromyalgia and chronic fatigue syndrome in 2017, 2019, or 2020-21. Tr. 54. It was her understanding that if you have RA, you will eventually have fibromyalgia and if you have fibromyalgia you will eventually get RA. "The two are somewhat linked." Tr. 54.

I asked petitioner about her lichen planus disease. She stated she developed sores and blisters in her mouth that were very painful after a hysterectomy in 2014. Her dentist sent her to an oral surgeon who sent her to UMDNJ where she was told she had burning mouth syndrome that caused some gum recession and the blisters all over her mouth. It eventually went away after 7 months. She does not have gingivitis.[42] Tr. 55.

E. Petitioner's Husband's Testimony

Petitioner's husband, Mr. Mehl, testified. He has been an IT analyst at Morristown Medical Center for 34 years. He stated that currently petitioner does not work but did work full time or 35 hours a week as a vet tech which was physically demanding. Tr. 58-61. Following her injury from the Tdap vaccine, she spent a few months going to doctors. Her injury progressed and she could not work anymore which he believed was in August of 2017. Tr. 62.

Mr. Mehl recalled that petitioner received the tetanus vaccine at an urgent care after she cut her finger cooking. Tr. 62-63. Prior to that, she was in good health, busy with two children, the house and working full time. Tr. 63. She had back issues from a car accident in 2003, but no other health conditions. Tr. 63-64. She never complained of joint pain or muscle pain before the vaccination. Tr. 64.

He "guessed" the night of the vaccination she mentioned that she did not feel well, her arm hurt and was red and swollen. Tr. 64. In the days that followed she didn't feel well, her whole body

[42] The medical records indicate that she developed lichen planus after strep and multiple rounds of antibiotics in 2015. Pet. Ex. 24 at 10; Pet. Ex. 11 at 1-2; Pet. Ex. 12.

ached, and her arm was still swollen. He stated that he never saw her have a reaction to a vaccine like that before. Tr. 65. She got progressively worse, her joints and tendons were swelling, and she was very achy. Tr. 65-66. She was "definitely sick". Tr. 67. She went to several doctors but initially no one could help her. Tr. 67. She became frustrated with Dr. Efros when he couldn't tell her what was wrong with her other than saying that she got sick from the shot. Tr. 67-68.

Mr. Mehl stated that petitioner got sick right away after the shot because he recalled that it ruined Christmas. He stated it also made that winter tough because he had to take care of the children and the house and work overtime because the petitioner stopped working. Petitioner took the children to school, went to doctors' appointments, and mainly took care of herself. Tr. 68-69. Before the vaccine, she did everything. All of her symptoms were related to the September 2016 Tdap vaccination. The medical bills piled up and no one was able to tell her what was going on. Tr. 70-71. She is doing better now but still can't work. Tr. 71.

Mr. Mehl stated that petitioner had back issues from a car accident, went to pain management, took prescribed medication and had fentanyl patches. Her back pain did not stop her from working. Tr. 73-74. He only recalled her taking off from work to have their children, for a foot surgery, and for a hysterectomy, but she always went back to work full time. Tr. 74-75. She never had to go on disability or unemployment or anything like that before the tetanus vaccine. Tr. 77. He did not recall her being out of work in 2014 for active EBV. Tr. 77-78.

Mr. Mehl did not recall petitioner having any joint or muscle pain unrelated to her back, seeing Dr. Efros, or being told she had pre-clinical RA prior to her receipt of the Tdap vaccine. Tr. 75-76.

IV. Expert Opinions

A. Qualifications

i. Petitioner's Expert, Eric Gershwin, MD

Dr. Gershwin is well known to the Court and has been recognized as an expert in internal medicine, rheumatology, and allergy and clinical immunology in which he holds board certifications. Pet. Ex. 28 at 2. He has been a Professor of Medicine, specializing in Rheumatology and Allergy, at the University of California, Davis since 1981 and Chief of the Division of Rheumatology/Allergy and Clinical Immunology since 1982. *Id.* at 1. Dr. Gershwin's curriculum vitae lists numerous books, book chapters, and research papers of which he is a listed author. *See id*. at 8–125.

Dr. Gershwin submitted four expert reports in this case. Pet. Ex. 27; Pet. Ex. 58; Pet. Ex. 60; Pet. Ex. 80.

ii. Respondent's Expert, Mehrdad Matloubian, MD, PhD

Dr. Matloubian is also well known to the Court and has been recognized as an expert in rheumatology in which he is board certified. He has taught at the University of California, San Francisco since 2001 and is currently an "HS Clinical Professor" of Medicine in the Division of

Rheumatology. Resp. Ex. B at 1-2. Dr. Matloubian has published several peer-reviewed articles alongside other authors. *Id*. at 10-14. He is also a practicing clinician. *Id*. at 3.

Dr. Matloubian also has a Ph.D. in virology/immunology and has been engaged in research in this area for more than twenty years. Resp. Ex. A at 1. His areas of expertise include T and B cell responses, especially to viruses as well as factors that regulate lymphocyte circulation and trafficking. Throughout most of his research career, he has focused on innate and adaptive immune responses to acute and chronic viral infections. *Id*.

Dr. Matloubian submitted three expert reports in this matter. Resp. Ex. A; Resp. Ex. C; Resp. Ex. D.

B. Opinions

i. Dr. Gershwin's Opinion

Dr. Gershwin opined that the Tdap vaccination petitioner received on September 12, 2016 was the "final pathway that led from a pre-clinical phase of disease, to the clinical onset of rheumatoid arthritis" and accelerated the onset of clinical disease by 2.25/2.5 years.[43] Pet. Ex. 27 at 1; Pet. Ex. 60 at 4. Dr. Gershwin clarified that he was not saying that the Tdap vaccine caused or significantly aggravated petitioner's RA, only that it accelerated the onset of clinical disease by 2.5 years. Pet. Ex. 27 at 1; Tr. 90. He stated she would have developed RA, but there was no prediction of when. Pet. Ex. 60 at 2; Tr. 133-36.

Dr. Gershwin explained that RA is an autoimmune disease that attacks the peripheral joints, such as the hands, fingers, wrists, elbows, shoulders, feet, knees, and back, and occurs predominantly in women. Its development starts with genetic susceptibility that can remain asymptomatic or preclinical for years until an environmental trigger(s) initiates the final pathway from preclinical to clinical disease. Pet. Ex. 27 at 2; Pet. Ex. 58 at 1-2; Tr. 87-89. Seropositive RA has autoantibodies to CCP or RF. Seronegative RA has the same symptoms but no autoantibodies. Tr. 88. Dr. Gershwin stated that the etiology of autoimmune disease is a combination of "bad genes and bad luck." Tr. 88. Smoking, bad gums, and certain organisms in the teeth and gut are major risk factors for the induction of RA, but as with most autoimmune diseases, it is difficult to tell whether it is the genes or the environment that initiated the disease. Tr. 89.

Dr. Gershwin relied on *Goodnow* to explain the multistep pathogenesis leading to autoimmunity in general, which includes inherited and somatic mutations that lead to loss of tolerance along with various mechanisms including bystander activation, production of proinflammatory cytokines, alterations of nucleic acid sensors, and final disruption of T and B regulatory pathways for the emergence of clinical disease, with the potential that more than one pathway may be involved. Pet. Ex. 27 at 2-5; Pet. Ex. 30;[44] Tr. 92-93. *Goodnow* explains that T and B lymphocytes of the immune system are equipped with different receptors for detecting antigens. T lymphocytes express T cell receptors and B cells express B lymphocyte receptors

[43] In some places, Dr. Gershwin uses 2.25 years and in others he uses 2.5 years.
[44] Christopher C. Goodnow, *Multistep Pathogenesis of Autoimmune Disease*, 130 CELL 25 (2007), filed as "Pet. Ex. 30".

which power cell growth and initiate survival pathways when faced with an antigen. "Activation of these pathways by antigen triggers clonal lymphocyte proliferation, mobilizing immunity against infection." Uncontrolled activity of these cells promotes disease. Pet. Ex. 30 at 1. The growth of self-reactive lymphocytes is normally blocked by a series of checkpoints; autoimmunity develops when these checkpoints are bypassed. *Id*. at 4, 6. Several environmental factors over a lifetime are necessary to tweak the immune system of a genetically susceptible individual until the final emergence of clinical disease. Succinctly, environmental factors trigger exaggerated immune responses in genetically predisposed individuals causing final disruption of T and B regulatory pathways. Pet. Ex. 27 at 1, 4; Pet. Ex. 29;[45] Pet. Ex. 30; Pet. Ex. 60 at 2-3; Tr. 118-20.

Dr. Gershwin acknowledged that in RA a finding of positive anti-CCP marks the initial loss of tolerance, and the long road to autoimmunity ensues with the eventual onset of clinical illness. Tr. 117. Dr. Gershwin stated that *Goodnow* was "seminal" to his opinion that petitioner's positive anti-CCP testing in 2014 was the biomarker for her evitable development of RA but it would not predict when she would develop RA. Pet. Ex. 60 at 2; Tr. 133-36. He discussed the prolonged period of latency between when autoantibodies appear and the subsequent onset of clinical disease. He noted that sera from healthy individuals shows latent RA up to 10 years before symptom onset. Pet. Ex. 27 at 1-2, 4; Pet. Ex. 29;[46] Pet. Ex. 30;[47] Tr. 92. Therefore, Dr. Gershwin proposed that the median time for the onset of clinical disease following the detection of autoantibodies is 4.5 years based on clinical studies. Pet. Ex. 27 at 4. Using the date of the Tdap vaccine as the time of onset, ". . . If we take a 50% point, the assumption would be that [petitioner's] autoantibodies were present for 2.25 years before she received the tetanus vaccination. Therefore, she would have developed rheumatoid arthritis within a period of 2.25 years after September 12, 2016 whether she was vaccinated or not." Dr. Gershwin concluded that petitioner's onset of clinical RA was 2.25 years sooner than it would have been because of the Tdap vaccination. *Id*.

In a subsequent report, Dr. Gershwin relied on clinical studies to show that patients with positive anti-CCP and a family history of RA had onset of clinical disease on average within 5 years. He reasoned that since petitioner tested positive for anti-CCP in 2014, her onset of clinical disease in 2016 was 2.5 years sooner than it would have been if not for the Tdap vaccine. Pet. Ex. 60 at 4. "…I cannot say for sure that it would not have developed 6 months later" but literature shows that patients who are anti-CCP positive and have arthralgias develop RA within 3-4 years. Pet. Ex. 80 at 2. He quoted from *Karlson*, which discussed RA as a multi-hit process with the more hits acquired, the greater the risk of developing clinical disease, as supportive of his opinion that petitioner developed clinical RA 2.5 years sooner than she would have as a result of an "environmental 'hit' that was the Tdap vaccination". Tr. 143-45; Pet. Ex. 75 at 1, 3;[48] Pet. Ex. 80 at 2-3. He argued that his conclusion was not based on statistics but "rooted in [his] own vast experience with RA and its diagnoses and clinical presentation. Medical literature, as cited in [his] reports and testimony, support this conclusion and timing." Pet. Ex. 80 at 3. Further, "[j]ust because [petitioner] *could* have developed RA on her own shortly after she did *without* vaccination, does not change the fact she *did develop* RA when she did more likely than not *because of* her

[45] Selmi et al., *supra* note 4.
[46] *Id*.
[47] Goodnow, *supra* note 44.
[48] Karlson et al., *supra* note 15.

vaccination as the 'hit' that broke tolerance". *Id*. (emphasis in original). He admitted his 2.5-year figure was "somewhere between an estimate and a guess." Pet. Ex. 60 at 4.

Dr. Gershwin acknowledged that RA affects 1% of women and is more common in those who smoke. He agreed that petitioner had a genetic predisposition, tested positive for autoantibodies to CCP in 2014, smoked, and was in the preclinical phase of RA at the time she received the Tdap vaccination on September 12, 2016. Pet. Ex. 27 at 4-5; Pet. Ex. 30.[49]

He submitted *Criswell*, which was referred to as the "twin study" during hearing and stated that the presence of RA in identical twins was only around 25%. This means that the remaining 75% of twins involve one twin with RA and one twin without. This shows that there are factors beyond just genetics that are involved in the development of RA. In fact, most patients with RA—even those with family history of RA—go through several phases of increased risk, beginning with genetic predisposition then various exposures, including from environment, lifestyle, and behavior. Pet. Ex. 60 at 1-2; Tr. 141-42; Pet. Ex. 72.[50] Dr. Gershwin described the phases of RA, which include an asymptomatic phase, evidence of immune activation phase (i.e. positive CCP or RF), arthralgias phase, and the final phase of definable synovitis or swollen joints. Tr. 138-39. Many events over a lifetime challenge the immune system until it becomes activated by cytokines to the point where clinical disease appears. Those with "strong genetic predisposition" will not require as many events. Tr. 93.

Dr. Gershwin stated that *Karlson* also showed that genetic and multiple environmental factors including hormones, diet, infections, and tobacco all drive the immune system before the appearance of clinical RA. Tr. 137-38; Pet. Ex. 74.[51] *Karlson* noted that a gene and epitope has been identified in the mechanistic pathway and smoking can modify the structure of CCP proteins increasing the chances of developing RA if one has the genes. Tr. 140. Even if a patient stopped smoking like petitioner here, it would not negate the risk factor of developing RA. Tr. 140.

He relied on *Ridgley* to show the existence of cytokine perturbations (or disruptions) before the clinical onset of rheumatoid arthritis, some of which have been linked to activation of autoantibodies, suggesting that cytokines may trigger a transition from systemic immunity to arthritis. Pet. Ex. 58 at 1; Pet. Ex. 59.[52]

Dr. Gershwin argued that the Tdap vaccination was the final "somatic factor" in petitioner's development of clinical RA. Tr. 140-41. He relied on *Symmons* which discussed case reports involving various vaccines precipitating arthritis in individuals. Dr. Gershwin then stated that there are so many factors over the years and no one gene or event that can be pinpointed as the specific defining event for clinical disease because of individual differences. Tr. 145-48, 154; Pet. Ex. 71.[53]

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[49] Goodnow, *supra* note 44.
[50] L.A. Criswell et al., *Smoking Interacts with Genetic Risk Factors in the Development of Rheumatoid Arthritis Among Older Caucasian Women*, 65 ANNALS OF THE RHEUMATIC DISEASES 1163 (2006), filed as "Pet. Ex. 64" and "Pet. Ex. 72".
[51] Karlson & Deane, *supra* note 14.
[52] Laura A. Ridgley et al., *What are the Dominant Cytokines in Early Rheumatoid Arthritis?*, 30 CURRENT OPINION IN RHEUMATOLOGY 207 (2018), filed as "Pet. Ex. 59".
[53] Symmons, *supra* note 19.

Initially, Dr. Gershwin claimed that petitioner suffered "serum sickness like disease" from the Tdap vaccine with myalgias and arthralgias reflective of a heightened immune response mediated by proinflammatory cytokines. He described these cytokines as the key players in the differentiation and expansion of pathogenic autoantibodies to CCP with Tdap vaccine serving as the final somatic event that led to the acceleration of petitioner's RA onset. Pet. Ex. 60 at 2, 3. He later clarified that cytokines drive the immune response in RA which is why RA treatment targets cytokines and not the antibodies of RF or CCP. Tr. 104-09. Here, the receipt of the Tdap vaccine initiated cytokine production increasing inflammatory markers and acted as the driver and final environmental trigger that led to the onset of clinical RA 2.25 years earlier than it would have otherwise; anything beyond the vaccination was the natural progression of the RA. Pet. Ex. 27 at 4; Pet. Ex. 60 at 3.

Dr. Gershwin conceded there is no defined metric for when RA will clinically manifest but argued that the issue here is whether an environmental stimulus such as a Tdap vaccine can facilitate the transition from pre-clinical to clinical RA. Pet. Ex. 58 at 1; Tr. 154. In his opinion, the Tdap was the final trigger accelerating the onset of disease. Tr. 148. He could not say when her disease onset would have occurred if not for the Tdap vaccine. Pet. Ex. 60 at 4. He acknowledged that there is no literature that states vaccinations can accelerate the development of clinical RA. Tr. 153-54. He agreed that no infection has been definitively found to cause RA, other than chronic EBV and gingivitis which have been shown to play a role. Tr. 154-55. He agreed that studies show observed elevated cytokines, chemokines, and acute phase reactants 2-12 years prior to the clinical onset of RA. He agreed that the literature does not provide a specific cytokine level or threshold that needs to be reached for the transition to clinical RA. He stated that every individual is different, so autoantibody levels are not telling because someone can have severe disease with only mildly elevated antibodies or vice versa. Tr. 160-61. He acknowledged that *Goodnow* did not discuss vaccinations as an environmental cause or accelerator of RA in either animals or humans with genetic predisposition. Tr. 157. He further agreed that *Goodnow* concluded that progression from latent to measurable autoimmunity did not require external triggers such as infection and that the study showed autoimmunity occurring in germ free animals who had a specific mutation so that infection was not required, it was dietary exposure. Tr. 157, 159; Pet. Ex. 30;[54] Pet. Ex. 37 at 2.[55]

Dr. Gershwin concluded that petitioner had genetic predisposition, smoked, was anti-CCP positive since 2014 and would have developed clinical RA at some point. However, she was in a preclinical phase of RA when she received the Tdap vaccine which acted as the final straw in the environmental link of events producing clinical disease. The mechanisms of bystander activation, production of proinflammatory cytokines, alterations of nucleic acid sensors, and/or final disruption of T and B regulatory pathways reflect the multi-step pathogenesis in autoimmunity with the Tdap vaccine serving as the final "hit" to move from pre-clinical to clinical RA, 2.5 years sooner than she would have otherwise become symptomatic. Pet. Ex. 27 at 2-5; Tr. 92. Petitioner would not have developed symptomatic RA when she did but for the Tdap vaccination. Tr. 124-

[54] Goodnow, *supra* note 44.

[55] Michael A. Maldonado et al., *The Role of Environmental Antigens in the Spontaneous Development of Autoimmunity in MRL-lpr Mice*, 162 J. IMMUNOLOGY 6322 (1999), filed as "Pet. Ex. 37".

25. "[C]learly, I'm hedging here . . . All I can say for sure is that she [] would not have developed it on that day. I think 2.4 or 2.5 years is a reasonable way to start." Tr. 125-26.

ii. Dr. Matloubian's Opinion

Dr. Matloubian disagreed with Dr. Gershwin's opinion in this case. Resp. Ex. D at 1, 2-3, 4; Resp. Ex. C at 1, 3; Resp. Ex. A at 9. He defined RA as a systemic inflammatory disease manifesting as peripheral arthritis mainly in the small joints of the hands and feet, affecting about 1% of the Caucasian population, mostly women, with peak onset between 50 and 75 years of age. Resp. Ex. A at 5; Tr. 173-75; Resp. Ex. A Tab 3.[56] Generally, a diagnosis of inflammatory arthritis is made after excluding a host of other conditions and diseases which may present with similar symptoms. Resp. Ex. A at 5; Tr. 178-80. Clinical diagnosis includes physical examination of the joints for objective evidence of joint inflammation. Tr. 176-78; Resp. Ex. A Tab 3 at 13-14. RA patients can present with insidious onset of pain, stiffness, and swelling in multiple joints over weeks to months or have a fulminant presentation. Resp. Ex. A at 5.

Dr. Matloubian discussed the pathogenesis of RA as not well understood, the significance of anti-CCP antibodies, and that both genetic and environmental factors contribute to the development of clinically apparent RA. Further, it is well established that the development of autoantibodies (CCP and/or RF) are the hallmarks of RA, signal the breakdown of immune tolerance, and occur silently in patients, years before symptom onset. Petitioner was anti-CCP positive in 2014, signaling that her immunological tolerance was broken at that time and therefore, the vaccine could not have been the "hit that broke tolerance" as suggested by Dr. Gershwin. Resp. Ex. A at 7; Resp. Ex. D at 3; Resp. Ex. A Tab 4;[57] Resp. Ex. C Tab 1[58]; Pet. Ex. 80.

Further, Dr. Matloubian pointed out that Dr. Gershwin's opinion in this case was contrary to his own writings on autoimmunity which include that, "[t]he initial events triggering the onset of autoimmune disease invariably go unnoticed . . . By the time a clinical diagnosis is established, it is impossible to trace its origin back to any single event or even cluster of events." Resp. Ex. D at 3; Resp. Ex. D Tab 1.[59] Dr. Gershwin's writings and the literature Dr. Matloubian cited show that autoimmunity and the factors that drive the transition from pre-clinical to clinical autoimmunity begin years before a diagnosis. Resp. Ex. D at 3-4; Resp. Ex. C Tab 1 at 7.[60] Therefore, Dr. Matloubian argued that Dr. Gershwin's theory that the inflammatory cytokines induced by the Tdap vaccine acted as a final hit that led to petitioner's clinical RA is not supported by any literature, including Dr. Gershwin's own literature. Resp. Ex. D at 4.

Dr. Matloubian submitted that the cause of autoantibody development and what causes the transition to clinically apparent RA is unknown. Tr. 183-84; Resp. Ex. A at 8; Resp. Ex. A Tab

[56] Imboden et al., *supra* note 18.
[57] Vivianne Malmström et al., *The Immunopathogenesis of Seropositive Rheumatoid Arthritis: From Triggering to Targeting*, 17 NATURE REV. IMMUNOLOGY 60 (2017), filed as "Resp. Ex. A Tab 4".
[58] Deane & Holers, *supra* note 5.
[59] Andrea T. Borchers, PhD et al., *How to Outfox Mother Nature – Autoimmunity: Moving From Shadows to Sunshine*, 2 ISRAEL MEDICATION ASSOCIATION J. 15 (2000), filed as "Resp. Ex. D Tab 1".
[60] Deane & Holers, *supra* note 5.

13.[61] While some autoimmune diseases like Guillain-Barre Syndrome occur after acute infection, the majority of autoimmune diseases are not associated with infection. Tr. 186-87. RA has not been associated with any acute infection, but it has been associated with chronic infections such as EBV and gingivitis. Tr. 187. There is no literature to support tetanus, diphtheria, or pertussis bacteria being associated with RA. Tr. 187-88.

Dr. Matloubian agreed that RA is a multistep process involving multiple phases from genetic predispostion to clinical onset of disease, but the factors important to each phase are not completely understood. Tr. 188-93; Resp. Ex. A at 7; Resp. Ex. C Tab 1.[62] It is known that environmental factors such as smoking, antibiotic use, and those with specific genes[63] are at a higher risk for developing RA. Smoking in general but especially in conjunction with having HLA DRB1 positivity increases the risk of anti-CCP positivity and the development of RA. Resp. Ex. A at 7-8; Tr. 184.

Dr. Matloubian added that the long latency period between the development of autoantibodies and the onset of clinical disease makes it difficult to establish a causal link between any environment exposure or to rule out random immunologic events. Most epidemiological data show an association but not a causal link. Resp. Ex. A at 8.

Dr. Matloubian referred to recent studies which have addressed the role of autoimmunity and inflammation in mucosal sites open to the environment such as lungs, gastrointestinal tract, and the mouth now believed to play a role in the pathogenesis of RA. The studies suggest that changes in the bacterial composition of mucosal sites such as periodontal disease play a causal role during at-risk periods in development of RA and may contribute to its pathogenesis. Resp. Ex. A at 8. A recent study showed a strong association between antibiotic usage in children and the development of juvenile idiopathic arthritis, suggesting that alteration in gut microbiome from repeated antibiotic use may affect self-tolerance in genetically susceptible people, rather than external infections as previously thought. *Id.*; Resp. Ex. A Tab 15.[64]

Dr. Matloubian noted that petitioner had a history of smoking, oral lichen planus (an autoimmune disease involving her mouth), and took multiple courses of antibiotics, all of which could have affected her stomach microbiome and changed the balance of her immune system leading to the progression from pre-clinical to clinical RA. Resp. Ex. A at 9; Pet. Ex. 9 at 1; Pet. Ex. 11 at 3; Pet. Ex. 24 at 4, 9, 11-12. Further, petitioner tested positive for anti-CCP in 2014 and

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[61] Kevin D. Deane, *Autoantibodies, Citrullinated Histones and Initiation of Synovitis*, 11 NATURE REVIEWS RHEUMATOLOGY 688 (2015), filed as "Resp. Ex. A Tab 13".

[62] Deane & Holers, *supra* note 5.

[63] Alleles (genes) for RA include HLA-DR4, an MCH class molecule, which displays peptides (pieces of proteins) to T cells that respond to antigens. Tr. 184-85. HLA alleles associated with RA bind to citrulline peptides (an amino acid) strongly. Citrulline is not a naturally appearing amino acid meaning when proteins are made, citrulline is not contained therein. When a protein is made, there's an enzyme called "PAD", which changes arginine (a different amino acid) into citrulline. It is believed that smoking upregulates PADs, which in turn makes citrulline in the lungs which then interact with HLA risk alleles in people with RA. Tr. 185. Distinguishing seropositive and seronegative RA is important for pathogenesis and treatment because more is known about the genetic and environmental factors for seropositive than seronegative RA. Tr. 179-80; Resp. Ex. A Tab 4 (smoking is important for seropositive RA but not seronegative).

[64] Daniel B. Horton, MD, MSCE et al., *Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case-Control Study*, 136 PEDIATRICS e333 (2015), filed as "Resp. Ex. A Tab 15".

was already developing RA at least two years before the vaccination. While a strong link between smoking and RA has been shown, no link has been shown between vaccinations and the development of RA. Resp. Ex. A at 9.

Dr. Matloubian concluded that the Tdap vaccine did not accelerate the onset of petitioner's RA because: 1. No data exists that indicates how long it takes a person who is anti-CCP positive to develop symptomatic RA; 2. factors that lead from pre-clinical RA to symptomatic clinical RA are unknown and no trigger has been identified for the transition; 3. multiple controlled studies have shown that vaccinations do not lead to the development of RA or otherwise accelerate the disease onset; and 4. based on controlled studies, vaccinations are recommended for patients with pre-exiting RA and have not been found to aggravate disease severity in those with clinical RA. Resp. Ex. A at 9.

He discussed the literature relied on by Dr. Gershwin noting that *Goodnow* discussed genetic mutations in the immune regulatory pathways as the somatic events that lead to the development of autoimmunity—not environmental exposures as stated by Dr. Gershwin. Resp. Ex. A at 10; Resp. Ex. D at 4; Pet. Ex. 30.[65] *Goodnow* did not discuss vaccinations as either an environmental cause or accelerator in the development of autoimmunity in animals or people with genetic predisposition. Resp. Ex. A at 10. The authors found that "[t]he event(s) that trigger progression from latent to measurable autoimmunity in Fas-deficient mice do not involve an external trigger such as infection because autoimmunity occurs equally in germ-free animals". *Id*. The study suggests that external triggers such as infection or vaccination are not necessary to lead to autoimmunity in genetically susceptible people. *Id*.; Pet. Ex. 30 at 5.

Further, *Maldonado* tested the hypothesis that normal stimulation of the immune system occurring from environmental stimuli, whether infectious or dietary, was necessary for the initiation and/or continuation of autoimmunity but found no data to support a role for infectious agents in the induction of lymphoproliferation and B cell autoimmunity in the mice studied. Resp. Ex. A at 10; Pet. Ex. 37 at 2.[66]

Likewise, *Fomin* concluded that influenza vaccine did not lead to worsening of RA symptoms. Resp. Ex. A at 10; Resp. Ex. A Tab 17.[67] *Bengtsson*, a study in Sweden that included 1998 cases of RA and 2252 age matched controls followed for five years after vaccination, found no association between seropositive (anti-CCP positive) or seronegative RA and vaccine exposure. Further, there was no increased risk in the highest risk group being smokers or carriers of HLA-DRB2 shared epitope alleles. Resp. Ex. A at 10; Resp. Ex. A Tab 18.[68] Further, the authors found no association between the receipt of multiple vaccines and an increased risk of developing RA, supporting the notion that multiple stimulation of the immune system does not "accelerate" the rate of RA and weighing against Dr. Gershwin's theory that multiple environmental stimuli can accelerate the development of RA. Resp. Ex. A at 10-11; Tr. 205-07.

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[65] Goodnow, *supra* note 44.
[66] Maldonado et al., *supra* note 55.
[67] I. Fomin et al., *Vaccination Against Influenza in Rheumatoid Arthritis: The Effect of Disease Modifying Drugs, Including TNFα Blockers*, 65 ANNALS OF THE RHEUMATIC DISEASES 191 (2006), filed as "Resp. Ex. A Tab 17".
[68] Camilla Bengtsson et al., *Common Vaccinations Among Adults Do Not Increase the Risk of Developing Rheumatoid Arthritis: Results from the Swedish EIRA Study*, 69 ANNALS OF THE RHEUMATIC DISEASES 1831 (2010), filed as "Resp. Ex. A Tab 18".

Further, *Westra* summarized several studies on vaccine safety and efficacy in RA and other autoimmune diseases showing no onset or increased disease activity following vaccination. Tr. 204; Resp. Ex. A Tab 22.[69] *Ray*, a large Kaiser cohort, looked at vaccines including tetanus vaccine, and found no increase of RA. Tr. 204-05; Resp. Ex. A Tab 16.[70] The American College of Rheumatology recommends flu vaccine to patients with autoimmune diseases including RA both before and after initiation of immunosuppressive therapy. Resp. Ex. A at 11-12; Resp. Ex. A Tab 23.[71]

After distinguishing case studies from control studies, Dr. Matloubian noted that there was no evidence of association of autoimmunity found following viral vaccines in either. Resp. Ex. A at 11; Resp. Ex. A Tab 19;[72] Resp. Ex. A Tab 20.[73] Two studies that focused on lupus showed that without a control group, the data could be interpreted as being representative of cause and effect with vaccination leading to exacerbation of lupus, but with a control group, the results showed that exacerbation was a random occurrence and not causally related to immunization. Resp. Ex. A at 11; Resp. Ex. A Tab 21.[74]

Dr. Matloubian submitted that despite extensive studies, no association between vaccinations and RA has been found and no progression from preclinical RA to clinical disease from vaccination has been shown. Resp. Ex. A at 12.

Dr. Matloubian referenced *Deane*, a 2019 study which states, "[W]ith the understanding that RA-related autoimmunity begins years before the onset of incident inflammatory arthritis, it is therefore highly likely that factors that trigger and propagate RA-related autoimmunity, as well as drive the transition from pre-RA to inflammatory arthritis are acting years before a diagnosis." Tr. 191; Resp. Ex. C Tab 1 at 7.[75] The environmental factors that appear to increase an individual's risk for transitioning from an autoantibody positive pre-RA to clinical RA include smoking, obesity, and perhaps microbiome; these are all ongoing and chronic, unlike an acute infection or vaccination. Tr. 192; Resp. Ex. C Tab 1 at 7. In short, the rheumatology research community accepts that clinically apparent RA takes years to develop before a person presents with joint swelling. Tr. 192-93. None of the literature filed in this case mentions vaccinations or an acute event such as an acute infection in the pathogenesis of RA. Tr. 193; Resp. Ex. A at 10; Resp. Ex. D at 4. This argues against Dr. Gershwin's theory that the Tdap vaccination was the trigger for the transition from preclinical to clinical RA. Tr. 192.

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[69] Johanna Westra et al., *Vaccination of Patients with Autoimmune Inflammatory Rheumatic Diseases*, 11 NATURE REVIEWS RHEUMATOLOGY 135 (2014), filed as "Resp. Ex. A Tab 22".
[70] Paula Ray et al., *Risk of Rheumatoid Arthritis Following Vaccination with Tetanus, Influenza and Hepatitis B Vaccines Among Persons 15-59 Years of Age*, 29 VACCINE 6592 (2011), filed as "Resp. Ex. A Tab 16".
[71] Jasvinder A. Singh et al., *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*, 68 ARTHRITIS CARE & RESEARCH 1 (2015), filed as "Resp. Ex. A Tab 23".
[72] Symmons, *supra* note 19.
[73] Ami Schattner, *Consequence or Coincidence? The Occurrence, Pathogenesis and Significance of Autoimmune Manifestations After Viral Vaccines*, 23 VACCINE 3876 (2005), filed as "Resp. Ex. A Tab 20".
[74] G.W. Williams, M.D., Ph.D. et al., *Influenza Immunization in Systemic Lupus Erythematosus*, 88 ANNALS OF INTERNAL MEDICINE 729 (1978), filed as "Resp. Ex. A Tab 21".
[75] Deane & Holers, *supra* note 5.

Dr. Matloubian agreed that cytokines are involved in the development of RA but there is no data to suggest that a transient rise in cytokines following a vaccine or acute infection can trigger the onset of clinical RA three months later. Tr. 194-96; Resp. Ex. A at 10; Resp. Ex. D at 4. The literature refers to chronic inflammation or chronic low level cytokine production over time leading to tissue and joint damage ultimately leading to the onset of symptomatic RA, not as "trigger" in the sense being used by Dr. Gershwin. Tr. 196-97; Resp. Ex. D at 4; Resp. Ex. C Tab 1.[76] Therefore, petitioner's progression from pre-clinical to symptomatic RA was unrelated to her vaccinations. Resp. Ex. A at 12-13.

Finally, Dr. Matloubian addressed Dr. Gershwin's opinion that Tdap vaccine accelerated the onset of petitioner's clinical RA by 2.5 years. Resp. Ex. A at 12-13. Dr. Matloubian pointed out that petitioner tested anti-CCP positive in November of 2014, although it was unknown how long before 2014, she may have been positive. *Id.*; Tr. 202, 215-17. The literature shows that people can test positive for anti-CCP up to 10 years before they develop clinical RA and on average 3-5 years before they have clinically detectible inflammatory arthritis. Tr. 203. Relying on a study that used 4.5 years based on a range from .1-13.8 years and without knowing when petitioner's anti-CCP positivity began, Dr. Gershwin concluded that petitioner transitioned to clinical RA 2.25 years sooner than she otherwise would have if she did not receive the Tdap vaccine, which is "quite speculative and quite a guess." Tr. 203; Pet. Ex. 56.[77] Dr. Matloubian did not agree that a time frame for when she would have developed RA can be calculated. Tr. 203. There is no literature to substantiate Dr. Gershwin's conclusion regarding the acceleration of clinical RA and no metric that exists to determine how long a person is autoantibody positive before transitioning to active disease. Resp. Ex. A at 12-13.

Dr. Matloubian disagreed that the Tdap (or flu vaccine) played any role in the onset of petitioner's clinical RA. Resp. Ex. A at 9, 14.

V. Legal Standard

A petitioner is required to establish their case by a preponderance of the evidence. 42 U.S.C. § 300aa-13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [they] 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 & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing a special master's decision that petitioners were not entitled to compensation); *see also Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357 (Fed. Cir. 2000); *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with the dissenting judge's contention that the special

[76] Deane & Holers, *supra* note 5.

[77] Alexander Egle et al., *VavP-Bcl2 Transgenic Mice Develop Follicular Lymphoma Preceded by Germinal Center Hyperplasia*, 103 BLOOD 2276 (2004), filed as "Pet. Ex. 56".

master confused preponderance of the evidence with medical certainty). At the same time, mere conjecture or speculation is insufficient under a preponderance of evidence standard. *Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984).

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. 42 U.S.C. § 300aa-11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii); *see also Wright v. Sec'y of Health & Human Servs*., 22 F.4th 999, 1006 (Fed. Cir. 2022) (defining the term "residual effects" in the Act, as "detrimental conditions within the patient, such as lingering or recurring signs and symptoms" of the alleged vaccine injury, which are compensable). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Petitioners are not required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs*., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of eliminating alternative independent potential causes"). Once a petitioner has proven causation by preponderant evidence, "the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs*., 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa-13(a)(1)(B)).

To prove causation, a petitioner must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that a petitioner show by preponderant evidence that a vaccination they received caused their 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. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each *Althen* prong requires a different showing. Under the first prong, a petitioner 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 (citation omitted). To satisfy this prong, a petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu*, 569 F.3d at 1379 (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id*. at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs*., 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). Even if the vaccination can cause the injury, a petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs*., 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *Id*. at 961 (citation omitted), and "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," *Paluck v. Sec'y of Health & Human Servs*., 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375).

The third *Althen* prong requires that a petitioner establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id*. However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id*.; *see also Locane v. Sec'y of Health & Human Servs*., 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

Finally, although this decision discusses some but not all the literature in detail, I have reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human 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 & Human 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).

VI. Discussion

The experts herein agreed more than they disagreed. They agreed that petitioner had pre-clinical RA, was anti-CCP positive since at least 2014, and would have eventually developed

clinical RA with or without the Tdap vaccine. Pet. Ex. 27 at 1; Pet. Ex. 60 at 2; Resp. Ex. D at 3. They agreed that RA is a multi-phase/stage disease that starts with genetic predisposition and has a long latency period between the appearance of autoantibodies and the development of clinical symptomatology. Pet. Ex. 27 at 2; Resp. Ex. A at 7, 8; Resp. Ex. D at 3-4; Tr. 93, 117, 192-93. They agreed that there is no well-defined metric to calculate when clinical disease will begin after the appearance of autoantibodies. Pet. Ex. 58 at 1; Resp. Ex. A at 12-13; Tr. 203. They ultimately agreed that petitioner did not suffer from "serum sickness" following either her Tdap or influenza vaccinations. Pet. Ex. 60 at 2; Resp. Ex. C at 6.

Prior to and during the hearing, Dr. Gershwin maintained that the arthralgias and myalgias petitioner complained of following the Tdap vaccine were symptoms associated with the Tdap vaccine and not RA. Pet. Ex. 60 at 2; Tr. 106-07. In a supplemental report issued following the hearing, Dr. Gershwin opined that petitioner's complaints of arthralgias and myalgias following the Tdap vaccination were symptoms of RA because pain is often the initial symptom of RA. Pet. Ex. 80 at 1-2. Whether the arthralgias and myalgias suffered immediately following the Tdap vaccine were related to the Tdap vaccine or RA dictates whether Dr. Gershwin is opining that petitioner's onset of clinical or symptomatic RA was within hours of the Tdap vaccine or three months later when synovitis or joint swelling was first noted on medical examination by Dr. Efros. This is addressed in Prong III below.

All three *Althen* prongs are at issue in this case.

A. *Althen* Prong I

Under the first prong of *Althen*, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994).

Dr. Gershwin was clear. It was not his opinion that the Tdap vaccine caused or significantly aggravated petitioner's RA because she would have ultimately developed clinical RA with or without the vaccination. His opinion is only that the Tdap vaccine accelerated petitioner's transition from preclinical RA to clinical RA by 2.5 years. Pet. Ex. 27 at 1; Pet. Ex. 60 at 4; Tr. 90.

Dr. Gershwin's theory included that the proinflammatory cytokines elicited in response to the Tdap vaccination were the key players in the differentiation and expansion of pathogenic autoantibodies to CCP and served as the final environmental trigger necessary to accelerate the transition from preclinical to clinical RA 2.5 years sooner than symptomatic RA would have otherwise occurred. Tr. 90, 92; Pet. Ex. 27 at 1; Pet. Ex. 58 at 2; Pet. Ex. 60 at 3-4. His theory required the presence of persistent myalgias and arthralgias from vaccination through December of 2016, reflecting the systemic or heightened immune response mediated by the pro-inflammatory cytokines elicited from the Tdap vaccination. Pet. Ex. 60 at 2, 3-4; Pet. Ex. 80 at 1-2. He initially opined that petitioner suffered serum sickness following the Tdap vaccination but later agreed that

she did not. Pet. Ex. 60 at 2. After the hearing, he opined that the arthralgias and myalgias following the Tdap vaccination were the first symptoms of clinical RA. Pet. Ex. 80 at 1-2.

Dr. Gershwin maintained that *Goodnow* was seminal to his opinion because it showed the activity of T and B lymphocytes in the immune system when faced with an antigen and how autoimmunity can occur when that system fails. Pet. Ex. 27 at 2-5; Pet. Ex. 30 at 1, 4, 6;[78] Tr. 92-93. Further, *Goodnow* showed how multiple mutations—inherited or acquired—can lead to the emergence of autoimmune disease driven by various cytokines and that environmental factors can trigger an exaggerated immune response in genetically predisposed individuals causing the final disruption of T and B regulatory pathways, resulting in autoimmunity. Pet. Ex. 27 at 1, 4; Pet. Ex. 29;[79] Pet. Ex. 30; Pet. Ex. 60 at 2-3; Tr. 118-20, 123.

Dr. Gershwin stated that RA is cytokine not autoantibody driven. Tr. 104-09. Therefore, the Tdap vaccination can initiate cytokine production that accelerates clinical onset of the disease even though RA would have developed eventually. Pet. Ex. 27 at 4; Pet. Ex. 60 at 3. He agreed that anti-CCP positivity marks the initial loss of tolerance and begins the long road to autoimmunity before the eventual onset of clinical RA. Tr. 117. He conceded that *Goodnow* concluded that the progression from latent to measurable autoimmunity did not require external environmental triggers such as infection because the autoimmunity occurred in the study in germ free animals. Tr. 157, 159; Pet. Ex. 30;[80] Pet. Ex. 37 at 2.[81] He further agreed that *Goodnow* did not address vaccines. Tr. 157.

Dr. Gershwin referenced case reports to show that various vaccinations can precipitate arthritis in some individuals. However, he conceded that RA is the result of interactions between susceptible hosts and many unidentified environmental factors over several years, with no single gene, combination of genes, or environmental event pinpointed as the defining event for transition to clinical disease. Tr. 87-89, 93, 45-48, 154; Pet. Ex. 27 at 2; Pet. Ex. 58 at 1-2; Pet. Ex. 71.[82] He agreed that studies show that elevated cytokines, chemokines, and acute phase reactants are active in RA 2-12 years prior to clinical onset of disease. Tr. 160-61. He agreed that no literature provides a specific cytokine threshold level that needs to be reached for the development of clinical RA. Tr. 104-09, 160-61. He agreed that no literature discussed vaccinations or infections causing or accelerating RA in a genetically susceptible animal or human. However, he argued that the studies were underpowered for traditional epidemiology in a disease like RA where multiple environmental and somatic events are involved. Tr. 153-55, 259; Pet. Ex. 60 at 2-3. In response to there being no literature that shows that infection with tetanus, diphtheria, or pertussis bacteria is associated with RA, Dr. Gershwin stated that "…to conclude that vaccines can't cause an autoimmune disease because infectious agents don't seem to cause an autoimmune disease is not to look at the broad microbiology…". Tr. 187-88, 250-51. He agreed that vaccinating individuals who have clinical RA is appropriate because "the horse is already out of the barn" and the somatic push that led to clinical disease already happened. Tr. 246-47.

[78] Goodnow, *supra* note 44.
[79] Selmi et al., *supra* note 4.
[80] Goodnow, *supra* note 44.
[81] Maldonado et al., *supra* note 55.
[82] Symmons, *supra* note 19.

Dr. Gershwin stated that he provided a "mosaic" of good science to try and relate the Tdap vaccination to the onset of clinical RA, "[b]ut if we're looking for an epidemiologic study that says that people that are positive for CCP and have [a] reaction to a vaccine have this somatic event at this time, I would agree completely. There is no such study." Tr. 260.

Dr. Matloubian maintained that the cause of RA is unknown with no specific trigger identified. Tr. 183-84; Resp. Ex. A at 8; Resp. Ex. A Tab 13.[83] He stated that other than mentioning bystander activation and various other mechanisms known to be involved in autoimmunity, Dr. Gershwin did not explain how a transient increase in cytokines from a vaccine could "trigger" clinical RA. Tr. 194-96; Resp. Ex. A at 10; Resp. Ex. D at 4. Further, the term "trigger" when describing the progression of RA over time is not used in the sense that Dr. Gershwin is using it. Tr. 196-97; Resp. Ex. D at 4; Resp. Ex. C Tab 1.[84]

To that end, Dr. Matloubian referenced multiple studies that show the slow natural progression of RA involving increasing inflammation and tissue damage over time eventually manifesting into clinical disease. The progression does not require external stimuli—be it vaccine or infection. Tr. 192-93, 196-97; Resp. Ex. A at 10; Resp. Ex. D at 4; Resp. Ex. C Tab 1.[85] He agreed that some autoimmune diseases occur following acute infection but most chronic autoimmune diseases, like RA, are not associated with infection. Tr. 186-87. There is no literature that shows that infection with tetanus, diphtheria, or pertussis bacteria is associated with RA. Tr. 187-88. Epidemiology has not established causes or triggers for RA. Resp. Ex. A at 8.

Dr. Matloubian stated that the *Goodnow* study discussed genetic mutations as "somatic events" not environmental events as used by Dr. Gershwin. Tr. 221. While Dr. Matloubian agreed that vaccines elicit a transient increase in cytokines, he disagreed that a transient increase in cytokines could result in the transition from preclinical to clinical RA, stating that there is no support that a "one time hit" or any single event—be it vaccine or acute infection—is capable of causing the progression of pre-clinical RA to clinical RA. Tr. 192-93, 194-97; Resp. Ex. A at 10; Resp. Ex. D at 4.

Dr. Matloubian cited to *Deane* to show that cytokines have not been implicated in the transition from preclinical to clinical RA, but rather are present and active during the entire preclinical phase with an increase by the time of transition reflecting the natural progression of the autoimmune process. Resp. Ex. D at 3; Resp. Ex. C Tab 1;[86] Pet. Ex. 59 at 4.[87] *Deane* showed that a single event cannot trigger the transition from preclinical to clinical RA but it is "highly likely that factors that trigger and propagate RA-related autoimmunity, as well as drive the transition from pre-RA or inflammatory arthritis are acting years before a diagnosis." Tr. 191; Resp. Ex. C Tab 1 at 7.[88]

[83] Deane, *supra* note 61.
[84] Deane & Holers, *supra* note 5.
[85] *Id*.
[86] *Id*.
[87] Ridgley et al., *supra* note 52.
[88] Deane & Holers, *supra* note 5.

Dr. Matloubian stated that the only environmental factors or infections that have been shown to be associated with the development of clinical RA are those that are chronic such as smoking (with a 40-fold increased risk of RA), obesity, and bacterial infections such as gingivitis and chronic EBV. Tr. 187, 192; Resp. Ex. C Tab 1 at 7. The literature shows that clinical RA results from multiple environmental factors acting over the course of years in a person who is genetically predisposed. Pet. Ex. 71;[89] Pet. Ex. 74;[90] Resp. Ex. A Tab 6 at 1.[91] Even the "the twin study"—relied on by Dr. Gershwin to support his opinion that multiple environmental factors play a role in RA even in those with genetic predisposition—did not suggest that cumulative environmental factors were necessary to develop RA. Tr. 220-21; *see* Pet. Ex. 72.[92] Dr. Matloubian explained that identical twins have different immune systems with one twin potentially having more or different exposures throughout their life, such as smoking. The study merely showed environmental factors are involved in the development of RA—not that cumulative environmental factors are necessary as suggested by Dr. Gershwin. Tr. 220-21. To suggest that a single exposure like a vaccination or acute infection can cause the onset or transition to clinical disease in RA is speculative. Tr. 224-25.

Dr. Matloubian added that at-risk patients are advised to get vaccinated because there is no increase in clinical disease seen following vaccination, thus refuting the argument that a vaccine can cause the progression of RA from preclinical to clinical or accelerate onset. Resp. Ex. A at 9; Resp. Ex. C at 3-4; Pet. Ex. 30 at 5;[93] Resp. Ex. A Tab 16;[94] Resp. Ex. A Tab 17;[95] Resp. Ex. A Tab 18;[96] Resp. Ex. A Tab 22;[97] Resp. Ex. A Tab 23.[98] *Westra* summarized several studies on vaccine safety in RA and other autoimmune diseases and showed no onset or increased disease activity following vaccination. Tr. 204; Resp. Ex. A Tab 22.[99] *Ray* looked at vaccines, including tetanus vaccine, as triggers and found no increase of RA following vaccination. Tr. 204-05; Resp. Ex. A Tab 16.[100] *Bengtsson* found no association between seropositive (anti-CCP positive) or seronegative RA and vaccine exposure and no increased risk of RA overall in the RA group or control group. Resp. Ex. A at 10; Resp. Ex. A Tab 18.[101] Further, the authors found that giving multiple vaccinations at the same time showed no increased risk of developing RA, weighing against Dr. Gershwin's theory that the cumulative effect of multiple environmental stimuli is the acceleration of the development of RA. Tr. 205-07; Resp. Ex. A at 10-11.

Petitioners are not required to provide epidemiological evidence or scientific certainty to carry their burden in proving prong one, but they "must proffer trustworthy testimony from experts who can find support for their theories in medical literature in order to show causation". *LaLonde*, 746 F.3d at 1341; *see also Snowbank Enter.*, 6 Cl. Ct. at 486; *Moberly*, 592 F.3d at 1322; *de Bazan*,

[89] Symmons, *supra* note 19.
[90] Karlson & Deane, *supra* note 14.
[91] Hunt & Emery, *supra* note 21.
[92] Criswell et al., *supra* note 50.
[93] Goodnow, *supra* note 44.
[94] Ray et al., *supra* note 70.
[95] Fomin et al., *supra* note 67.
[96] Bengtsson et al., *supra* note 68.
[97] Westra et al., *supra* note 69.
[98] Singh et al., *supra* note 71.
[99] Westra et al., *supra* note 69.
[100] Ray et al., *supra* note 70.
[101] Bengtsson et al., *supra* note 68.

539 F.3d at 1351. Petitioner here has failed to provide preponderant evidence of a sound and reliable theory demonstrating how the Tdap vaccination "triggered" the transition from pre-clinical RA to clinical RA. The evidence presented supports the contrary: no single event has been shown to cause the transition from preclinical to clinical RA and studies have failed to show any increase in RA symptoms following vaccination. As such, petitioner failed to satisfy *Althen* prong one.

B. *Althen* Prong II

Having found that petitioner failed to provide a sound and reliable theory to support the Tdap vaccination accelerating the transition of petitioner's preclinical RA to clinical RA, the analysis could end here. However, to be thorough, the remaining prongs will be addressed.

To satisfy the second prong of *Althen*, a petitioner must establish 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 need only be "logical and legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49; *accord Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326(Fed. Cir. 2006).

The experts agreed that petitioner was anti-CCP positive since at least 2014, had pre-clinical RA, and would have ultimately developed RA at some point in time. They agreed she had multiple risk factors including smoking, being female, and having a positive family history. Pet. Ex. 27 at 1-2; Pet. Ex. 58 at 1; Resp. Ex. A at 2, 5, 9; Resp. Ex. D at 1-2.

Petitioner also had an autoimmune disease (excoriated lichen planus with lesions in her mouth that flared), chronic EBV with flares, and ongoing complaints of joint pain, stiffness, and fatigue since at least 2012. *See generally* Pet. Ex. 2; Pet. Ex. 4; Pet. Ex. 7; Pet. Ex. 8; Pet. Ex. 10; Pet. Ex. 24. While the experts agreed that petitioner was in the preclinical stage of RA since at least 2014 when she tested positive for anti-CCP antibodies, they parted ways in their opinions regarding petitioner's transition to clinical RA. Dr. Gershwin opined that the proinflammatory cytokines elicited from the Tdap vaccination caused a systemic or heightened immune response evidenced by myalgias and arthralgias and accelerated petitioner's transition to clinical RA by 2.25/2.5 years. Dr. Matloubian opined that having tested positive for anti-CCP in 2014, her course and transition to clinical RA was consistent with the natural progression of the disease and the vaccine played no role. Pet. Ex. 2 at 339; Pet. Ex. 27 at 2-5; Resp. Ex. A at 9.

Dr. Gershwin's arguments are unsupported. First, the medical records and petitioner's reporting do not support her suffering from persistent myalgias and arthralgias indicative of a systemic or heightened immune response to the Tdap vaccine that lasted for three months until she presented with the first clinical symptoms of RA (synovitis or joint swelling). Second, it is unknown when petitioner became anti-CCP or RF positive or what caused the elevated ESR and CRP on September 16, 2016. Third, Dr. Gershwin's opinion that the vaccine accelerated the onset of petitioner's RA by 2.25/2.5 years is speculative.

i. Persistence of petitioner's myalgias and arthralgias signifying a systemic or heightened immune response for over three months following the Tdap

vaccination is unsupported by the medical records or petitioner's own reported history.

Initially, Dr. Gershwin opined that petitioner suffered from persistent myalgias and arthralgias indicative of a systemic immune response caused by proinflammatory cytokines elicited from the Tdap vaccination which acted as the final trigger in transitioning her preclinical RA to clinical RA. Tr. 90, 92; Pet. Ex. 27 at 1; Pet. Ex. 60 at 2, 3-4; Pet. Ex. 58 at 2; Pet. Ex. 80. Dr. Gershwin stated that the persistence of these symptoms was necessary to support his theory that the Tdap vaccine caused ongoing proinflammatory cytokines that produced inflammation, the positive RF and ultimately resulted in the transition from pre-clinical to clinical RA. Pet. Ex. 60 at 2, 3-4; Pet. Ex. 80 at 1-2; Tr. 111-12.

In his report, Dr. Gershwin opined that petitioner's myalgias and arthralgias were due to low levels of immune complex formation. Pet. Ex. 60 at 2. During the hearing, he stated that her myalgias and arthralgias resulted from a systemic response caused by proinflammatory cytokines elicited by the Tdap vaccine. Tr. 106-07. Following the hearing, he opined that the arthralgias and myalgias were symptoms of RA because she complained of pain, and pain is one of the first symptoms of clinical RA. Pet. Ex. 80 at 1-2.

Dr. Matloubian disagreed. He explained that immune complexes from a small amount of antigen contained in a vaccine cannot be formed within 24 hours. Further, to form immune complexes, there would have to be enough pre-existing antibodies to the antigen and there was no evidence in this case to suggest that petitioner had long lasting immunity to Tdap with a high level of circulating antibodies to Tdap components sufficient to induce immune complexes more than 10 years after her last Tdap vaccination. Resp. Ex. A at 14; Resp. Ex. C at 6.

More importantly, the medical records and petitioner's reports to her treating physicians do not corroborate Dr. Gershwin's opinion of persistent myalgias and arthralgias. Therefore, his opinion fails to explain how the Tdap vaccination caused persistent elevation of proinflammatory cytokines sufficient to cause petitioner's transition to clinical RA roughly three months later. Even after he changed his opinion following the hearing that her arthralgias, myalgias and pain within 24 hours of vaccination were the first symptoms of clinical RA, he provided no explanation for how the proinflammatory cytokines elicited from a vaccine could do so. Further, Dr. Gershwin ignored or failed to address petitioner's ongoing complaints of myalgias and arthralgias, as well as joint and muscle stiffness, for years prior to September 12, 2016. Most importantly, Dr. Gershwin agreed at hearing that the medical records did not support that petitioner suffered "persistent" arthralgias and myalgias following her vaccinations. Tr. 129.

The medical records herein support a history of chronic EBV with several flares, as well as fatigue, joint and muscle pain, joint and muscle stiffness, and body aches resulting in a referral to rheumatologist Dr. Efros in October of 2014 and a finding of anti-CCP positivity in November of 2014. Pet. Ex. 2 at 339; Pet. Ex. 4 at 163-68; Pet. Ex. 23 at 1; Pet. Ex. 24 at 5-7. Her records further show that she frequently complained of joint and muscle pain and stiffness, as well as muscle swelling, throughout 2015 and 2016 prior to receiving the subject Tdap vaccine. Pet. Ex. 4 at 53, 70, 84, 91, 98, 105, 118, 124, 130, 136, 142, 168. In fact, just twelve days before the Tdap

vaccine, on August 31, 2016, review of systems was positive for back pain, joint pain, joint stiffness, muscle spasms, and muscle stiffness. *Id*. at 53.

Following the receipt of the Tdap vaccination through and including her visits with pain management on December 7, 2016 and with Dr. Efros on December 29, 2016 when joint inflammation was first noted, petitioner did not report persistent arthralgias and myalgias to her medical providers. Pet. Ex. 4 at 43, 46 (on September 28, 2016 she reported "feeling much better" and had no joint swelling, pain, or stiffness); Pet. Ex. 24 at 13 (also on September 28, 2016 she received a flu vaccine); Pet. Ex. 24 at 13-14 (there was then a gap in the records until November 9, 2016 when she reported joint pain and swelling, but no swelling was seen on examination); Pet. Ex. 23 at 2 (on December 29, 2016, she presented to Dr. Efros and reported receipt of a Tdap vaccine, "immediate generalized achiness followed by swelling of her left thumb, DIP and left second and third anterior MCP's," improvement, receipt of a flu vaccine on September 28, okay until November when "the same thing happened with her left thumb and left foot," immediate improvement with a prednisone taper, okay again until 12 days ago when she had a URI and "the same symptoms in her left thumb and left foot" developed.).

Neither petitioner nor her PCP seemed concerned about her complaints following the Tdap vaccination because she presented for and received a flu vaccine on September 28, 2016. It is unlikely that she would have presented for the flu vaccine or that her physician would have administered one had she had continuing complaints associated with the Tdap vaccination. Therefore, it is reasonable to conclude that whatever symptoms petitioner suffered following the Tdap vaccine were transient and resolved by September 28, 2016, when she presented for a flu vaccine.

Further, petitioner's reports to her physicians after the Tdap vaccination included joint pain mostly involving her left thumb and foot, the same complaints she made following the flu vaccine and a URI. Pet. Ex. 4 at 36; Pet. Ex. 23 at 2; Pet. Ex. 24 at 13. She reported more global symptoms in the years prior to the Tdap vaccination. Pet. Ex. 4 at 53, 70, 84, 91, 98, 105, 118, 124, 130, 136, 142, 163-68; Pet. Ex. 24 at 7.

Dr. Gershwin stated that the persistence of petitioner's myalgias and arthralgias was crucial to his opinion that the Tdap vaccine caused ongoing proinflammatory cytokines that produced immune complexes, RF, and inflammation, ultimately resulting in the transition from pre-clinical to clinical RA. Pet. Ex. 80 at 1-2. However, as the medical records and Dr. Gershwin's own admission at hearing reveal, this is unsupported by the record. Tr. 129.

ii. Petitioner's transition to clinical RA is not supported by the blood work results following the Tdap vaccination.

Dr. Gershwin relied heavily on petitioner's bloodwork, discussing the values before and after the Tdap vaccination to support his opinion that the Tdap vaccination generated inflammation sufficient for the transition to clinical disease. He used a chart containing the values of lab results at hearing to illustrate their importance to his opinion of systemic response to the Tdap vaccination. *See* Pet. Ex. 77.

Dr. Gershwin first discussed the November 2014 blood work showing anti-CCP positivity which he attributed to both pre-clinical RA and active EBV infection at that time. Tr. 93-94, 101-02. He agreed that chronic EBV is considered a "somatic event" for RA and that petitioner had chronic EBV that became active at least three times since 2012. Tr. 102-03.

Dr. Gershwin stated "that [petitioner's] history of having arthralgias four days after the vaccination" was "consistent with a systemic immune response" and supported by the September 16, 2016 blood work showing anti-CCP and RF positivity and elevated ESR and CRP. He stated that the ESR and CRP values would not be elevated to the levels they were from an infected cut on her finger. Tr. 93-94, 103. Therefore, the anti-CCP, RF positivity, and elevated CRP and ESR supported his opinion that the Tdap vaccination caused a systemic production of cytokines that elevated her inflammatory markers (ESR and CRP) and accelerated her RF production. Tr. 108-09, 251-54.

In discussing the results for the September 30, 2016 blood work, Dr. Gershwin explained that ESR and CRP can go up or down rapidly because the half-life of cytokines is short which explains why the values were drastically lower on September 30—14 days later. RF is also responsive to inflammation and its value fell as well but he never explained how the Tdap vaccination could cause the production of RF in the first place. Tr. 104-05, 108-09, 149-51. Dr. Gershwin opined that the lab results were evidence that the Tdap vaccination acted as the "final somatic event" that accelerated petitioner's clinical RA onset. Tr. 108-09. He did not address how petitioner's September 30, 2016 results were normal for inflammatory markers and reduced RF two days after her receipt of a flu vaccine from which she claimed to have again suffered from "serum sickness."

Dr. Matloubian disagreed with the interpretation of the lab results. He referred to the ESR and CRP levels as "mildly elevated" on September 16 and resolved by September 30, indicating that there was only an acute, transient rise in cytokines. Resp. Ex. A at 14; Resp. Ex. D at 3. He added that CRP and ESR elevation could have been from her vaccination, the infected cut on her thumb, or both. Tr. 199. However, she received a flu vaccination on September 28 with normal inflammatory markers two days later, on September 30, 2016, despite her report of fever and swollen lymph nodes resulting from the flu vaccine. Tr. 199-200. Therefore, Dr. Matloubian argued that the lab results do not support Dr. Gershwin's opinion that petitioner suffered an ongoing systemic or heightened inflammatory response following the Tdap vaccine. Her lab results also suggested that she did not suffer from exaggerated response to vaccinations in general and the earlier elevation in inflammatory markers was likely due to her infected finger. Tr. 200-01.

Further, Dr. Matloubian agreed with Dr. Gershwin that RA patients may have positive anti-CCP and/or RF years before developing clinical RA and here, the last testing "we have is November of '14 when [RF] was negative". Tr. 92-93, 101, 107-08. Therefore, similar to the anti-CCP positivity, it is unknown when petitioner became RF positive. Even though Dr. Gershwin focused on the negative RF value in July 2014 and the positive value in September 2016 as significant, he also conceded that those values hold little meaning for disease presentation since one can have low values with significant disease or high values with no symptoms of clinical disease. Tr. 100, 131, 161.

I do not find Dr. Gershwin's opinions regarding the September 16, 2016 elevated ESR and CRP inflammatory markers to be persuasive to support an exaggerated systemic response to the Tdap vaccination significant enough to trigger the transition from pre-clinical to clinical RA. Tr. 94-95. In fact, petitioner's medical records show an elevated ESR value of 32 in July of 2013 in the context of gastrointestinal complaints. Pet. Ex. 24 at 2. Petitioner's ESR value following the Tdap vaccination on September 16, 2016 was 26 then normal on September 30, 2016—two days after the flu vaccine with a reported second episode of "serum sickness". Pet. Ex. 2 at 77, 79, 87, 90; Tr. 104-05, 108-09, 149-51, 199-201. In light of petitioner's ESR being 32 (range of 0-20) with a non-descript stomach ailment in 2013, the elevation of ESR to 26 four days after the vaccine and in the context of an infected finger does not support a systemic response to the Tdap vaccine. Pet. Ex. 24 at 2; Pet. Ex. 2 at 87. Further, her ESR and CRP were both normal two days after the flu vaccine in the context of a claimed event of serum sickness, suggesting that petitioner does not suffer from heightened immune responses to vaccinations. Pet. Ex. 2 at 77, 79; Tr. 199-201. The most that these values show are fluctuations in one's general inflammatory markers with no identifiable cause ascribed. *See also* Resp. Ex. A at 6 (ESR is elevated in RA in the presence of notable joint swelling on examination which was not noted here until late December of 2016).

Dr. Matloubian's explanation of the lab results was more consistent with petitioner's medical history. Petitioner has been anti-CCP positive since November of 2014, meaning she was in the pre-clinical phase of RA at least since then. Dr. Matloubian explained and the literature confirmed that once tolerance is broken, there is ongoing inflammation until that inflammation eventually affects the joints and becomes symptomatic. Pet. Ex. 2 at 339; Tr. 217; Resp. Ex. A at 7, 9; Resp. Ex. C at 2; Resp. Ex. C Tab 1.[102] Thus, petitioner was already developing RA long before she received the Tdap vaccine on September 12, 2016. As Dr. Gershwin agreed, it was only a matter of time before petitioner developed clinical RA, regardless of vaccination. Pet. Ex. 27 at 1; Pet. Ex. 60 at 4.

Deane showed that individuals are RF and anti-CCP positive before transitioning from preclinical to clinical RA. Resp. Ex. C Tab 1 at 1256-57. Thus, the fact that petitioner tested positive for anti-CCP and RF shortly after vaccination may have been entirely coincidental with her development of clinical RA. But even if I were to accept that she became RF positive after vaccination, Dr. Gershwin conceded that RF positivity does not predict onset or severity of clinical RA. Tr. 92-93, 154, 100, 131, 161. This point is underscored by petitioner's own lab results, showing that her RF values went from 24 on both September 30 and November 9, 2016, to 85 in December of 2016, then to 231 by July of 2017. Despite the much higher RF value in July of 2017, she was noted to have low RA activity. Pet. Ex. 3 at 23, 32, 37, 42; Pet. Ex. 16 at 151, 158.

In combination with petitioner's failure to provide a persuasive theory for how Tdap vaccine can accelerate the onset of RA, Dr. Gershwin's opinion that petitioner's lab results showed an exaggerated systemic response to the Tdap vaccine sufficient to cause RF positivity and transition from preclinical to clinical RA lacks any evidentiary basis and is therefore unpersuasive.

iii. Dr. Gershwin's opinion that the vaccine accelerated the onset of petitioner's RA by 2.25/2.5 years is speculative.

[102] Deane & Holers, *supra* note 5.

Dr. Gershwin conceded that petitioner would have eventually developed clinical RA, regardless of her receipt of the Tdap vaccination. His opinion is only that she transitioned to clinical RA 2.25/2.5 years earlier than she otherwise would have because of the Tdap vaccine. Pet. Ex. 27 at 1, 4; Pet. Ex. 60 at 4.

Dr. Gershwin initially proposed that the median time for the onset of clinical RA following detection of autoantibodies is 4.5 years based on clinical studies. Pet. Ex. 27 at 4. Using the date of vaccination with Tdap as the onset of clinical RA, Dr. Gershwin opined that, "…If we take a 50% point, the assumption would be that [petitioner's] autoantibodies were present for 2.25 years before the tetanus vaccination. Hence, she would have developed rheumatoid arthritis within a period of 2.25 years after September 12, 2016, whether she was vaccinated or not." *Id*. Later, he based his calculation on when anti-CCP was first detected, opining that her onset would have been 5 years later. Pet. Ex. 60 at 4. Thus, the vaccine accelerated the onset of clinical RA by 2.5 years. However, he also admitted that his 2.5-year figure was "somewhere between an estimate and a guess." *Id*.

Dr. Gershwin acknowledged that the preclinical period of RA is ongoing for years with many challenges to the immune system which activate cytokines until clinical disease appears. Tr. 92-93. He acknowledged that petitioner had other "somatic event[s]" throughout her life but argued that the Tdap vaccine was the "final somatic event" that forced the transition from preclinical RA to clinical RA and that she would not have developed clinical RA when she did but for the Tdap vaccination. Tr. 124-25. "[C]learly, I'm hedging here . . . All I can say for sure is that she [] would not have developed it on that day. I think 2.4 or 2.5 years is a reasonable way to start." Tr. 125-26.

Dr. Matloubian agreed that the preclinical phase of RA lasts for years before the inflammation results in joint swelling. Studies show that patients with preclinical RA have active low-level inflammation up to 12 years before the onset of joint swelling and the diagnosis of clinical RA. Resp. Ex. C at 2-3; Pet. Ex. 67 at 4.[103] The rheumatology research community accepts that clinically apparent RA takes years to develop before a person presents with joint swelling. Tr. 192-93. He disagreed that a single event or factor could act as a final "trigger" for the transition from preclinical RA to clinical RA, citing to literature that shows that the factors that "drive the transition from pre-RA to [inflammatory arthritis] are acting years before a diagnosis." Tr. 191-92; Resp. Ex. C Tab 1 at 7.[104] Rather, he submitted that there are environmental factors, such as smoking and microbiome, that are chronic and act over the course of years before clinical disease, not within a matter of days. Tr. 192; Resp. Ex. C Tab 1 at 7.

Dr. Matloubian added that the breakdown of immunological tolerance to specific antigens that leads to the formation of anti-CCP and pre-clinical RA had already occurred by the time petitioner received the Tdap vaccine. Resp. Ex. A at 7; Resp. Ex. C at 2. Further, even though she tested anti-CCP positive in November of 2014, it is unknown when before that she became anti-CCP positive. It could have been months or even years prior. Tr. 202-03. Studies show that people can test positive for anti-CCP up to 10 years before they develop clinical RA and on average 3-5 years before they have clinically detectible inflammatory arthritis. Tr. 203; Resp. Ex. A at 12;

[103] Karlson et al., *supra* note 15.
[104] Deane & Holers, *supra* note 5.

Resp. Ex. C at 2. Dr. Gershwin's reliance on a mean of 4.5 years without knowing when petitioner's autoantibody positivity began is "quite speculative and quite a guess." Tr. 203.

Further, Dr. Matloubian disagreed that a time frame for the development of clinical RA could be calculated. Tr. 203. There is no agreed-upon metric within the scientific community for how long it takes a person to develop clinical RA after becoming anti-CCP positive. Resp. Ex. A at 12; Resp. Ex. C at 1.

I find Dr. Gershwin's opinion to be unpersuasive and contrary to what the scientific community knows and what studies have shown about RA. The experts agree that petitioner was anti-CCP positive and in the preclinical stage of RA since at least 2014 and would eventually develop clinical RA. Pet. Ex. 27 at 1, 4; Pet. Ex. 60 at 4; Resp. Ex. A at 7; Resp. Ex. C at 2. Dr. Gershwin admitted that there is no metric for when clinical RA will present after becoming anti-CCP positive. Pet. Ex. 58 at 1. In his own words, the 2.25/2.5 years was "somewhere between an estimate and a guess." Pet. Ex. 60 at 4. Dr. Gershwin's opinion that the Tdap vaccine accelerated the onset of petitioner's clinical RA by 2.25/2.5 years fails to satisfy the preponderant evidence standard required by the Act. *See Snowbank Enter.*, 6 Cl. Ct. at 486; *Moberly*, 592 F.3d at 1322; *de Bazan*, 539 F.3d at 1351.

iv. Petitioner's treating physicians do not support a logical sequence of cause and effect between the Tdap vaccine and her clinical RA.

Generally, "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". *Paluck*, 786 F.3d at 1385 (internal citations omitted). However, special masters are directed to consider the evidence as a whole and are not bound by the notes of treating physicians within the medical record. *See Snyder ex rel. Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

As with expert testimony offered to establish a theory of causation, the opinions of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 742,749 (2011), *aff'd,* 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd,* 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion,* 475 F. Appx. 765 (Fed. Cir. 2012).

Dr. Gershwin and petitioner argue that Drs. Efros and Bartov believed the Tdap vaccination triggered or was involved in the onset of petitioner's clinical RA. Pet. Ex. 1 at 2-3; Pet. Ex. 58 at 1. However, the characterization of the doctors' records is not entirely accurate. Dr. Efros wrote on December 29, 2016, that he had a "[v]ery long discussion with patient about possible diagnoses and treatment options. RA? Relationship between tetanus shot and initiation of symptoms". Pet. Ex. 23 at 2. At a follow up appointment on January 25, 2017, Dr. Efros again documented discussing petitioner's diagnoses and treatment as "?early RA. ?reaction to DPT". *Id*. at 3. The record is unclear as to the meaning of Dr. Efros' notes, specifically whether he believed there was

a relationship between the Tdap vaccination and the onset of her symptoms, whether he simply documented what petitioner expressed to him, or whether he questioned if she had early RA as well as a reaction to the DPT.

Similarly, Dr. Bartov wrote following petitioner's first visit on February 8, 2017, "[s]uspected early RA given synovitis, positive RF and elevated acute phase reactants, possibly triggered by tetanus vaccine". Pet. Ex. 2 at 548. Again, depending on how that sentence is read, Dr. Bartov may have been questioning whether the "acute phase reactants" were triggered by the tetanus vaccine, not that the Tdap caused her synovitis and positive RF. Further, "possibly" does not rise to the level of preponderance. *See Moberly*, 592 F.3d at 1322; *de Bazan*, 539 F.3d at 1351.

Neither Dr. Efros nor Dr. Bartov made any definitive statements regarding the Tdap vaccine causing or accelerating her RA. Even if their records were interpreted as either Dr. Efros or Dr. Bartov opining that the Tdap vaccine was responsible for the onset of petitioner's clinical RA, they would not be entitled to much weight given that no evidentiary support was provided for that opinion.

v. Conclusion of Prong II

Dr. Gershwin's opinion that petitioner had persistent myalgias and arthralgias caused by proinflammatory cytokines elicited by the Tdap vaccine that produced RF and inflammation, ultimately resulting in the transition from pre-clinical to clinical RA was unsupported by the medical records. Pet. Ex. 80 at 1-2. Notably, Dr. Gershwin agreed at hearing that the medical records did not document persistent myalgias and arthralgias. Tr. 129. Importantly, by petitioner's own reporting to her providers, she had ongoing but intermittent complaints of joint pain and stiffness with improvement both before and after vaccination. Pet. Ex. 4 at 39, 43, 46, 53, 70, 84, 91, 98, 105, 118, 124, 130, 136, 142, 168; Pet. Ex. 23 at 2-3; Pet. Ex. 24 at 7.

Dr. Gershwin's opinion that petitioner's lab results supported an exaggerated systemic response to the Tdap vaccine sufficient to cause RF positivity and spark the transition from preclinical to clinical RA lacked any evidentiary basis and was unpersuasive. Summarily, the elevated ESR value of 26 on September 16 did not support an exaggerated systemic response to the Tdap vaccination when petitioner had ESR values higher than that during a non-descript stomach ailment in 2013. Pet. Ex. 24 at 2; Pet. Ex. 2 at 87. Further, two days after the flu vaccine, her ESR and CRP were both normal, suggesting that petitioner does not suffer from heightened immune responses to vaccinations. Pet. Ex. 2 at 77, 79; Tr. 199-201. Dr. Gershwin ultimately conceded that the presence of RF positivity does not predict onset or severity of clinical RA and it is unknown when petitioner became RF positive. Tr. 92-93, 100, 131, 154, 161.

Dr. Gershwin's opinion that petitioner transitioned to clinical RA 2.25/2.5 years sooner than she would have but for the Tdap vaccine based on her November 2014 positive anti-CCP test was admittedly "somewhere between an estimate and a guess." Pet. Ex. 60 at 4. It is unknown when petitioner became anti-CCP positive; even if that were known, Dr. Gershwin admitted that there is no metric for when clinical RA will present after becoming anti-CCP positive. Pet. Ex. 58 at 1; Tr. 202. Dr. Gershwin agreed that with or without the vaccine, she was going to develop RA

eventually. Pet. Ex. 27 at 1, 4; Pet. Ex. 60 at 4. Ultimately, Dr. Gershwin's opinion fails to reach the preponderant evidence standard required by the Act.

Likewise, neither Dr. Efros nor Dr. Bartov opined that petitioner's Tdap vaccine caused or accelerated her RA. Pet. Ex. 23 at 2-3; Pet. Ex. 2 at 548. As such, the notes contained in their medical records are insufficient to satisfy petitioner's burden.

Studies provide longstanding support for Dr. Matloubian's argument that it is unlikely that "a single pathogenetic mechanism could explain the occurrence of arthritis after a natural virus infection and after administration of an inactivated toxoid." Pet. Ex. 71 at 2.[105] More likely, multiple agents that acted over the course of years led to the immunological process that eventually manifested as clinical RA in petitioner in December of 2016. Pet. Ex. 23 at 2 (record from December 29, 2016 visit with Dr. Efros documenting joint swelling on physical examination for the first time); Pet. Ex. 71 at 1; Pet. Ex. 74 at 1;[106] Resp. Ex. A Tab 6 at 1.[107]

Petitioner has failed to demonstrate by preponderant evidence of a logical sequence of cause and effect that her development of clinical RA was caused and/or related to the Tdap vaccination. As such, she has failed to satisfy prong two.

C. *Althen* Prong III

The third *Althen* prong requiring an appropriate temporal relationship contains two parts. First, a petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and second, she must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Human Servs.,* 101 Fed. Cl. 532, 542-43 (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). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury utilized to satisfy the first prong. *Shapiro*, 101 Fed. Cl. at 542; *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).

I asked Dr. Gershwin at hearing to clarify onset based on petitioner's complaints of arthralgias and myalgias beginning the night of vaccination with no clinical proof of symptomatic RA until three months later. Dr. Gershwin stated that the myalgias and arthralgias were due to the Tdap vaccine—not to RA—and were persistent. Tr. 106-07, 149-50. The Tdap vaccination produced cytokines within 24 hours of vaccination, which drove the transition from preclinical to clinical disease, with synovitis ultimately appearing in December of 2016. He did not provide any explanation for how that transitionary process would take three months. Tr. 149-51.

In his supplemental report following the hearing, Dr. Gershwin opined that petitioner's pain following the Tdap vaccination was the onset of her clinical RA because pain—not synovitis—is often the first symptom of clinical RA. Pet. Ex. 80 at 2. He referenced two papers to

[105] Symmons, *supra* note 19.
[106] Karlson & Deane, *supra* note 14.
[107] Hunt & Emery, *supra* note 21.

support this opinion, arguing that her pain was "evidence of an ongoing process of RA developing clinical symptoms throughout September and October 2016 after vaccination, despite absence of specific complaints of joint swelling." *Id*. at 1-2; Pet. Ex. 81;[108] Pet. Ex. 82.[109]

He also referenced a conversation with petitioner's PCP in February 2022, claiming that the PCP described petitioner's "'generalized fatigue and joint pain'" on November 9, 2016 as his reason for prescribing a nine-day course of prednisone. Dr. Gershwin claimed that the dosage of prednisone was significant and reflected the PCP's concern for an ongoing inflammatory process. Pet. Ex. 80 at 1. Dr. Gershwin then wrote that "the onset of the 'generalized fatigue and joint pain' occurred a minimum of several days before November 9" when the PCP prescribed a nine-day course of prednisone and that this course of prednisone would have "significantly delayed" the onset of symptoms until she had joint swelling. *Id*. Dr. Gershwin provided no explanation for how her generalized fatigue and joint pain that occurred "a minimum of several days before" the November 9, 2016 visit was related to the Tdap vaccination she received nearly two months before or how a nine-day course of steroids beginning on November 9 would effectively suppress any clinical RA symptoms for almost two months thereafter. Further, this contradicted both his earlier opinion that her myalgias and arthralgias were ongoing since she received the Tdap vaccine or his later opinion that the symptoms were associated with the onset of RA within 24 hours of vaccination.

He concluded in this supplemental report that petitioner's generalized pain and fatigue "began shortly after vaccination in September 2016 and continued throughout the coming months until she was diagnosed with RA in December 2016, with symptoms both waxing and waning and being masked by steroids". Pet. Ex. 80 at 2. In stating that her symptoms waxed and waned, he contradicts his earlier opinion that her myalgias and arthralgias persisted from the day she received the Tdap vaccination through the time she presented with joint swelling in December 2016. This opinion is also seemingly inconsistent with his statement just one page prior in that report where he claimed petitioner's pain and fatigue "occurred a minimum of several days before November 9." *Id*. at 1. Dr. Gershwin provided no citations to the record in support of his opinion, nor did he provide any explanation as to why his opinion deviated from his initial reports and testimony.

Dr. Gershwin's report following the hearing was simply confusing. Regardless of when Dr. Gershwin places onset, he provided no explanation for how the Tdap vaccination could cause the transition to clinical RA within less than 24 hours or roughly three months later.

In Dr. Matloubian's opinion, based on what is known about the pathogenesis and etiology of RA, neither a vaccine nor an infection can cause, accelerate, or trigger the transition from pre-clinical to clinical RA. Resp. Ex. A at 8, 9-12; Resp. Ex. C at 3-4; Resp. Ex. D at 2. Further, RA is not rare so if 10,000 people get vaccinated, there is a 90% chance one will develop RA

[108] Diederik De Cock et al., *The Perspective of Patients with Early Rheumatoid Arthritis on the Journey from Symptom Onset Until Referral to a Rheumatologist*, 0 RHEUMATOLOGY ADVANCES IN PRACTICE 1 (2019), filed as "Pet. Ex. 81".

[109] Peter C Taylor, *Update on the Diagnosis and Management of Early Rheumatoid Arthritis*, 20 CLINICAL MEDICINE 561 (2020), filed as "Pet. Ex. 82".

coincidentally shortly thereafter. Still, a temporal relationship does not amount to causation. Tr. 225-26; *see also* Resp. Ex. C Tab 2.[110]

The experts agree and the literature supports that RA is a slow process that starts with genetic susceptibility, then the production of autoantibodies for the disease, followed by a long latent period of chronic, low-level inflammation that slowly destroys tissue, cartilage, and bone until there is sufficient damage to present clinically with swollen joints. Pet. Ex. 27 at 4; Pet. Ex. 60 at 3-4; Resp. Ex. A at 7-8; Resp. Ex. D at 4; Resp. Ex. C Tab 1.[111] This process can take up to 10 or more years. Pet. Ex. 75 at 4;[112] Resp. Ex. C Tab 1 at 5. There is no metric to determine when clinical RA will onset after becoming anti-CCP positive. Pet. Ex. 58 at 1; Resp. Ex. A at 12-13.

Petitioner failed to demonstrate that the onset of her clinical RA, either within 24 hours of the Tdap vaccination or roughly three months later in December 2016, was accelerated by or in any way related to the Tdap vaccination. Petitioner has failed to provide preponderant evidence to satisfy prong three.

VII. Conclusion

My sympathies go out to petitioner who lives with chronic pain from a host of conditions. But I cannot be guided by sympathy. Upon careful evaluation of all the evidence submitted in this matter, I find that petitioner has not shown by preponderant evidence that her vaccination was in any way related to the onset of clinical RA. Thus, she is not entitled to compensation under the Vaccine Act. **The Clerk shall enter judgment accordingly.**[113]

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master

[110] S. Sohail Ahmed et al., *Assessing the Safety of Adjuvanted Vaccines*, 3 SCIENCE TRANSLATIONAL MEDICINE 1 (2011), filed as "Resp. Ex. C Tab 2".
[111] Deane & Holers, *supra* note 5.
[112] Karlson et al., *supra* note 15.
[113] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party filing a notice renouncing the right to seek review.