In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: November 7, 2022

ANITA BURGESS,	*	PUBLISHED
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Petitioner,	*	No. 17-688V
	*	
v.	*	Special Master Nora Beth Dorsey
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus-Diphtheria-Acellular Pertussis ("Tdap") Vaccine; Pre-Existing Autoimmune Condition; Chronic Fatigue Syndrome ("CFS"); Connective Tissue Disease ("CTD"); Significant Aggravation.
Respondent.	*	

Renee Ja Gentry, The Law Office of Renee J. Gentry, Washington, DC, for Petitioner.
Austin Joel Egan, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On May 24, 2017, Anita Burgess ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2012)[2] alleging that she suffered significant aggravation of her pre-existing autoimmune condition as a result of a tetanus-diphtheria-acellular pertussis ("Tdap") vaccination administered to her on August 8, 2014. Petition at ¶ 16 (ECF No. 1). Respondent filed his Rule 4(c) Report on January 19, 2018, arguing "this case is not appropriate for

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (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 agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

compensation under the terms of the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 19).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has failed to provide preponderant evidence that her pre-existing autoimmune condition was significantly aggravated by her Tdap vaccination. Thus, Petitioner has failed to satisfy her burden of proof under Loving v. Secretary of Health & Human Services, 86 Fed. Cl. 135, 142-44 (2009). Accordingly, the petition shall be dismissed.

II. ISSUES TO BE DECIDED

First, the parties dispute diagnosis. Petitioner takes the position that she has an autoimmune condition "associated with a longstanding positive [antinuclear antibodies ("ANA")[3]] and a positive [Epstein-Barr virus ("EBV")]" that "has been alternately described as connective tissue disease [("CTD")], mixed connective tissue disease [("MCTD")], undifferentiated connective tissue disease [("UCTD")], chronic fatigue, [and] some kind of immunodeficiency." Petitioner's Motion for Ruling on the Record ("Pet. Mot."), filed Jan. 28, 2022, at 20 (ECF No. 102). While she agrees that her diagnosis does not "fit neatly into any category," she asserts that no specific diagnosis has been required for treatment purposes, and that her theory of causation does not turn on an "ultimate diagnosis." Id.

In response, Respondent argues that "[P]etitioner has not clearly established the injury for which she seeks compensation," and that it is "insufficient" to simple allege an "underlying autoimmune condition (whether termed [MCTD], [UCTD,] or chronic fatigue)." Resp. Response to Pet. Mot. ("Resp. Response"), filed Apr. 1, 2022, at 18-19 (ECF No. 105). Respondent bases this argument on the opinions of his experts. Drs. Erin Wilfong and Evan Anderson, who opined that each of these potential conditions are "unique and not interchangeable." Id. at 19. Thus, Respondent asserts that "establishing a differential diagnosis is a vital preliminary step for [P]etitioner to establish vaccine causation." Id. at 20.

Regarding causation, Petitioner asserts that her Tdap vaccination significantly aggravated her pre-existing autoimmune condition, and maintains that she has proven by preponderant evidence the standards articulated in Loving. Pet. Mot. at 14-33. Respondent disagrees. Respondent contends that Petitioner's claim fails because she has not satisfied her burden under the six-factor test established in Loving. Resp. Response at 18-29.

[3] Antinuclear antibodies are "antibodies directed against nuclear antigens; ones against a variety of different antigens are almost invariably found in systemic lupus erythematosus and are frequently found in . . . mixed connective tissue disease [("MCTD")]." Antinuclear Antibodies, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id =56804 (last visited Oct. 5, 2022).

III. PROCEDURAL HISTORY

Petitioner filed her petition on May 24, 2017, and medical records on May 26, 2017. Petition; Pet. Exhibits ("Exs.") 1-15. Additional medical records were filed from November 2017 to January 2018. Pet. Exs. 16-20. Respondent filed his Rule 4(c) Report on January 19, 2018, arguing "this case is not appropriate for compensation under the terms of the [Vaccine] Act." Resp. Rept. at 2.

Petitioner filed an expert report from Dr. Judy A. Mikovits and Dr. Francis W. Ruscetti on May 29, 2018. Pet. Ex. 21. Respondent filed an expert report from Dr. Erin M. Wilfong on October 15, 2018. Resp. Ex. A. On January 31, 2019, Petitioner filed an expert report from Dr. Joseph A. Bellanti. Pet. Ex. 48.

This case was reassigned to the undersigned in October 2019. Notice of Reassignment dated Oct. 8, 2019 (ECF No. 45). Petitioner filed additional medical records in October and December 2019. Pet. Exs. 58-59. On February 18, 2020, Respondent filed a supplemental expert report from Dr. Wilfong and an expert report from Dr. Evan J. Anderson. Resp. Exs. C, E. Petitioner filed a pre-hearing memorandum on March 9, 2020. Pet. Prehearing Memorandum ("Memo."), filed Mar. 9, 2020 (ECF No. 60).

The undersigned held a Rule 5 conference on March 10, 2020. Rule 5 Order dated Mar. 11, 2020, at 1 (ECF No. 61). At the Rule 5 conference, Petitioner indicated she is not relying on the expert report from Drs. Mikovits and Ruscetti or their medical literature.[4] Transcript ("Tr.") 5-6. Thereafter, Petitioner filed updated medical records in March 2020. Pet. Exs. 60-62. Respondent filed a pre-hearing brief on April 27, 2020. Resp. Pre-Hearing Brief ("Br."), filed Apr. 27, 2020 (ECF No. 72).

On May 6, 2020, the parties filed a joint status report, indicating the parties would like to proceed with a Ruling on the Record instead of an entitlement hearing in June 2020. Joint Status Rept., filed May 6, 2020 (ECF No. 77). Thereafter, Petitioner filed supplemental expert reports from Dr. Bellanti and updated medical records, and Respondent filed a supplemental expert report from Dr. Anderson. Pet. Exs. 63-66; Resp. Ex. H.

Petitioner filed a motion for a ruling on the record on January 28, 2022. Pet. Mot. Respondent filed his response on April 1, 2022, and Petitioner filed a reply on April 22, 2022. Resp. Response; Pet. Reply to Resp. Response to Pet. Mot. ("Pet. Reply"), filed Apr. 22, 2022 (ECF No. 106).

The matter is now ripe for adjudication.

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[4] Further, Petitioner did not reference this expert report or supporting medical literature in her briefs. See Pet. Prehearing Memo.; Pet. Mot.; Pet. Reply to Resp. Response to Pet. Mot. ("Pet. Reply"), filed Apr. 22, 2022 (ECF No. 106).

IV. MEDICAL TERMINOLOGY

A. Epstein-Barr Virus

Petitioner asserts that the Tdap vaccine triggered reactivation of her latent EBV, significantly aggravating her pre-existing autoimmune condition. Pet. Mot. at 14. EBV, a herpes virus, infects approximately 90-95% of adults. Pet. Ex. 50 at 3.[5] The primary infection generally occurs early in life, and the majority of cases are asymptomatic. Id. In adolescence or early adulthood, EBV infections can cause infectious mononucleosis. Id. After primary infection, once the infection is "controlled by the immune response, the virus remains latent for the lifetime of the host in B-lymphocytes." Id. The virus usually remains latent unless one is immunocompromised, has an HIV infection, or has drug-induced immunosuppression.[6] Id. at 7-8. "Occasional reactivation from latency and virus production is triggered by environmental stimuli but tightly controlled by the immune system of healthy individuals." Pet. Ex. 54 at 2.[7] "What triggers reactivation [of EBV] is not known precisely. The presumption is that it occurs when latently infected B cells respond to unrelated infections, because B-cell receptor stimulation triggers reactivation in B-cell lines." Pet. Ex. 55 at 3.[8]

Diagnosis can be confirmed by EBV-specific antibody[9] tests. Pet. Ex. 55 at 10. In "acute primary EBV infection," there will be Immunoglobulin M ("IgM") antibodies to the early viral capsid antigens ("VCA"). Id. After the onset of acute illness, from about the third week to the third month, VCA IgM antibodies decrease and VCA Immunoglobulin G ("IgG") antibodies increase and continue to be present throughout life. Id. After about six months, "VCA IgM antibodies disappear, and Epstein-Barr nuclear antigen 1 ("EBNA1") IgG antibodies become detectable and persist for life. All 3 antibodies may be present in late primary infection or subclinical reactivation . . . ." Id. EBV infection or reactivation can also be detected by polymerase chain reaction ("PCR") testing. Id.

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[5] Jason Aligo et al., Is Murina Gammaherpesvirus-68 (MHV-68) a Suitable Immunotoxicological Model for Examining Immunomodulatory Drug-Associated Viral Recrudescence?, 12 J. Immunotoxicology 1 (2015) .

[6] Aligo et al. did not identify any of Petitioner's illnesses as examples of those at risk for EBV reactivation. The authors also did not identify vaccines as associated with viral reactivation.

[7] Bettina Kempkes & Erie S. Robertson, Epstein-Barr Virus Latency: Current and Future Perspectives, 17 Current Ops. Virology 138 (2015).

[8] Oludare A. Odumade et al., Progress and Problems in Understanding and Managing Primary Epstein-Barr Virus Infections, 24 Clinical Microbiology Revs. 193 (2011).

[9] This Decision discusses various antibodies. An antibody is "an immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells), or with antigen closely related to it." Antibody, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=3261 (last visited Oct. 5, 2022).

B. Chronic Fatigue Syndrome

Chronic fatigue syndrome ("CFS") is "a multifaceted illness with a wide array of symptoms, potential etiological causes[,] and prognoses." Pet. Ex. 66 at 1.[10] Alternative names for the condition include myalgic encephalomyelitis, chronic fatigue immune disorder syndrome, and systemic exertion intolerance disease ("SEID"). Id. Criteria for CFS include "fatigue, neurocognitive dysfunction, disturbed sleep[,] and autonomic dysfunction." Id. at 2. The illness is characterized by "persistent and disabling fatigue that results in a significant reduction in activity for greater than six months" and "worsening of symptoms after mild physical and/or mental exertion." Id.

The cause of CFS is unknown, but there are a number of "popular hypotheses," which include infection, "microbiome disruption, immune response dysregulation, endocrine abnormalities[,] and intracellular dysfunction" in those who are "genetically susceptible." Pet. Ex. 66 at 2. There are two peak ages: between 10-19 years old and between 30-39 years old. Id. Additionally, CFS is more common in women. Id. A preceding infection is thought to be a risk factor, and the condition was first reported in association with fatigue following EBV infection. Id. at 3. "However, infection prior to its onset is not true of all [CFS] patients." Id. Further, "[a] wide range or microorganisms have been described in relation to CFS with varying mechanisms of pathogenesis." Id.

Diagnosis of CFS is difficult "due to lack of diagnostic testing" and "variability in its presentation and shared clinical symptoms with many conditions." Pet. Ex. 66 at 3. Moreover, "CFS is a diagnosis of exclusion, where it is important to rule out active diseases that share similar symptoms." Id. at 4. Clinical criteria for diagnosis include the "[p]resence of disabling fatigue for a minimum duration of 6 months in adults." Id. Fatigue "that affects both physical and mental functioning is an important indicator in diagnosis." Id. In addition, four of the following symptoms must be present: "memory problems, sore throat, post-exertion malaise, tender cervical or axillary lymph nodes, myalgia, multi-joint pain, headaches, and troubled sleep." Id. at 5. There are no abnormal laboratory tests or biomarkers required for diagnosis. Id.

C. Connective Tissue Disease, Undifferentiated Connective Tissue Disease, and Mixed Connective Tissue Disease

Connective tissue disease ("CTD") is an umbrella term encompassing both undifferentiated connective tissue disease ("UCTD") and mixed connective tissue disease ("MCTD"). Resp. Ex. A at 3. UCTD is "characterized by the presence of clinical and serological manifestations suggestive of autoimmune diseases but not sufficient to make a diagnosis of a defined CTD," such as systemic lupus erythematosus, Sjogren's syndrome, and

[10] Nazir Noor et al., A Comprehensive Update of the Current Understanding of Chronic Fatigue Syndrome, 11 Anesthesiology & Pain Med. e113629 (2021).

rheumatoid arthritis. Resp. Ex. A-1 at 1.[11] "[A] small percentage of patients with an undifferentiated onset, will evolve to defined CTDs while the majority of them will remain undifferentiated during the course of the disease." Id. at 2. Generally, UCTDs are "systemic autoimmune conditions characterized by a mild clinical profile and a simplified autoimmune repertoire. Although these conditions are generally benign, an evolution to CTDs is reported and changes in the disease course may occur." Id. at 3.

The characteristic symptoms of UCTD include arthritis, arthralgias, Raynaud's phenomenon, and leukopenia. Resp. Ex. A-1 at 2. Neurological symptoms and renal involvement are uncommon. Id. "About 90% of [] UCTD patients have [a] positive ANA" and 10-30% have anti-ribonucleoprotein ("anti-RNP") antibodies. Id. The majority of patients, however, have "a simple autoantibody profile characterized by a single antibody specificity." Id. There are no generally accepted diagnostic criteria for UCTD. Id. at 3. There are "[n]o triggering factors for the evolution of undifferentiated disease to defined CTDs [that] have been so far identified." Id. at 2.

MCTD is a condition characterized by "mixed features of systemic lupus erythematosus [], systemic sclerosis [], polymyositis/dermatomyositis [], and rheumatoid arthritis [] together with the presence of high-[titer] anti-U1 small nuclear (sn) [anti-RNP] antibodies." Resp. Ex. A-3 at 1.[12] MCTD can begin with a clinical presentation of any of the above identified illnesses at the time of onset or during the clinical course of the illness. Id. at 2. "The most common clinical features are polyarthritis, [Raynaud's phenomenon], sclerodactyly, swollen hands, muscle disorders[,] and [esophageal] dysmotility. Alopecia, malar rash, lymphadenopathy[,] or kidney damage are less common but can be present," and "fever, fatigue, arthralgias[,] or myalgias are also common." Id.

V. FACTUAL SUMMARY

A. Summary of Relevant Facts[13]

1. Pre-Vaccination Records

Petitioner was sixty-one years of age when she received a Tdap vaccine on August 8, 2014 in her left deltoid. Pet. Ex. 1 at 1. Her past medical history is notable for hysterectomy,

[11] M. Mosca et al., Undifferentiated Connective Tissue Diseases (UCTD), 6 Autoimmunity Revs. 1 (2006).

[12] Oscar-Danilo Ortega-Hernandez & Yehuda Shoenfeld, Mixed Connective Tissue Disease: An Overview of Clinical Manifestations, Diagnosis and Treatment, 26 Best Practice & Rsch. Clinical Rheumatology 61 (2012).

[13] This section is primarily taken from Respondent's Rule 4(c) Report. See Resp. Rept. at 2-10. Additional factual summaries are set forth in the parties' briefs. See Pet. Mot. at 2-8; Resp. Response at 4-14.

hormone replacement therapy, adrenal insufficiency, hypothyroidism, chronic fatigue, and post-traumatic stress disorder. Pet. Ex. 1 at 17-26; Pet. Ex. 19 at 71; Pet. Ex. 16 at 43.

More than two years before she received the vaccination at issue, on March 12, 2012, Petitioner's medical records documented complaints of fatigue and myalgias under review of systems. Pet. Ex. 16 at 43. On June 13, 2013, over a year before Petitioner received the Tdap vaccine, she was seen by primary care provider Amena Hashmi, D.O., at CareHere Clinic for a routine check-up. Pet. Ex. 1 at 20-21. Petitioner reported that she "ha[d] not been taking any thyroid medication or hydrocortisone [for] several months now. Hydrocortisone helps to eliminate fatigue, but because of side effects of steroids[,] [Petitioner] [did] not desire to take this medication." Id. at 21.

On July 18, 2013, Petitioner presented for an initial consultation with William Rea, M.D., of the Environmental Health Center-Dallas, complaining of a thirty-year history of fatigue and chronic infections. Pet. Ex. 5 at 28. Dr. Rea ordered labs, including ANA testing, which showed a positive ANA titer (1:40) with a homogenous pattern. Id. at 20. Dr. Rea also ordered a number of unconventional lab tests, including a urine screen for toxic metals, hair analysis for "Toxic & Essential Elements," a "Chlorinated Pesticides Profile," and a "Volatile Solvents Profile." Id. at 6-17. On July 29, 2013, Dr. Rea ordered an "autogenous vaccine"[14] for Petitioner. Id. at 18.

Over the next few months, Petitioner was seen by both Dr. Hashmi and Dr. Rea on multiple occasions. Pet. Ex. 1 at 18-20; Pet. Ex. 5 at 2-5, 41-67. On October 25, 2013, Petitioner saw treating physician, Stephen Dalton, D.O., at PNS Healthpoint Two. Pet. Ex. 6 at 46. Dr. Dalton noted, under history of present illness, that Petitioner "presents with [g]etting infections too easily and then needs antibiotics and then antifungals. She recently saw Dr. [Rea] in Dallas. She is on a sauna protocol and on supportive supplements. Now feeling so much better[.] Energy and clarity are now all better." Id. Petitioner wanted to discuss food allergies and fingernail infections. Id. She was taking estrogen and progesterone. Id. Physical exam revealed "fungal infection of some nails." Id. at 47. Dr. Dalton's diagnoses were reaction to food, bacterial vaginitis, menopause, and postmenopausal hormone replacement. Id.

On December 9, 2013, Petitioner saw another physician at CareHere Clinic, Filippo Masciarelli, M.D., for postmenopausal symptoms. Pet. Ex. 1 at 17-18. A few months later, on March 7, 2014, Dr. Dalton described Petitioner's recent history as follows:

> [Patient] is seeing Dr. [Rea] in Dallas - has had environmental lab testing - has been treating her with autogenous vaccine (whole blood) - also getting vaginal vaccine from the vaginal smear he did - using the bacteria he found - she states she is doing much better now - also sprained [right] ankle 5 [weeks] ago[,] seen in [emergency room ("ER")] - no fracture - continues to swell.

[14] An autogenous vaccine is "a vaccine prepared from a culture of microorganisms taken from the person to be treated with it." Autogenous Vaccine, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=116495 (last visited Oct. 5, 2022).

Pet. Ex. 6 at 39.

2. Vaccination and Post-Vaccination Records

Petitioner presented to CareHere Clinic on August 8, 2014, and saw Elizabeth Seymour, M.D. Pet. Ex. 16 at 60-62. Review of Systems was positive for fatigue. Id. at 60, 62. It was also noted that Petitioner "[h]as some type of immunodeficiency." Id. at 62. Dr. Seymour noted that Petitioner was seeing Dr. Rea, and she "[h]ad ANA + elevated 1:40 [titer] in the past." Id. at 61. She was reportedly "[t]rying diet, less carbs, no grains," and she wanted vitamin B12, vitamin D, and insulin, as well as a "complement differential performed." Id. Physical examination was normal. Id. Petitioner was given a Tdap vaccine. Id. at 62. Labs were ordered, including anti-RNP antibodies. Id.

Less than two weeks later, on August 20, 2014, Petitioner returned to Dr. Seymour, who reviewed the recent labs and noted,

> Cholesterol worse. Prediabetes improved. Also has positive RNP marker, for [CTD]. [Complains of] always being tired for 6+ months. Sometimes her joints ache, in hands, knees, and hips. Thinks she had a viral or possible reaction to the [Tdap] vaccine. [Complains of] fever, chills, aches, and fatigue. Now resolved.

Pet. Ex. 16 at 64. Physical examination was normal. Id. at 63. Dr. Seymour's diagnoses were "myalgia and myositis, unspecified" and "mixed hyperlipidemia." Id. at 64 (emphasis omitted). She was referred to rheumatology. Id.

On August 29, 2014, Petitioner saw Dr. Dalton for follow-up of her estrogen deficiency and medication refill. Pet. Ex. 6 at 30-31. Under Review of Systems, "[f]atigue" was noted with the additional comment that "[s]he has burned the candle at both ends for many years." Id. at 30. Upon review of the musculoskeletal system, it was noted that "[s]he tried a Cowden protocol[15] and everything hurt." Id. Physical examination revealed normal range of motion, normal strength, no tenderness, and minimal crepitus of the knees. Id. at 31. Dr. Dalton's diagnoses were menopause, postmenopausal hormone replacement, subclinical hypothyroidism, and chronic fatigue. Id.

Petitioner retuned to Dr. Hashmi on September 9, 2014, complaining of joint pain that "started after she got her Tetanus shot." Pet. Ex. 16 at 65. She reported night sweats, headaches, whole-body joint pain, fatigue, and crusty eyes. Id. The history also noted that Petitioner "believe[d] she's probably had symptoms of [MCTD] for several years, but believes after she got Tdap, it started a strong flare up that she can't seem to control." Id. Physical examination revealed tenderness in the metacarpophalangeal ("MCP") joints in both hands. Id. Dr. Hashmi prescribed a Medrol Dosepak. Id.

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[15] The Cowden protocol aims to "support immune system health, joint health, muscle and energy production as well as detox support" with the administration of various supplements. About the Program, NutraMedix, https://www.nutramedix.com/cowden-support-program-month-1.html (last visited Oct. 27, 2022).

One week later, on September 16, 2014, Petitioner saw rheumatologist Nuha R. Said, M.D., at the Medical Clinic of North Texas "at the request of Dr. Hashmi for evaluation of +ANA, +Sm[16] and RNP." Pet. Ex. 7 at 1. The following history was obtained by Dr. Said:

> States that about 30 years ago she had EBV and was very ill with that. However, despite intermittent flares of her EBV has been fairly healthy and active and has had only mild joint pain. She was well until she had her Tdap booster and states [that] the day after she developed severe swelling of her joints, red, hot, and swollen; had fevers, felt absolutely ill and did not improve significantly until she was started on a [M]edrol dosepack. However, she was nervous about using too much medication and has been taking Medrol 4 mg daily; feels that her hands in particular are still painful and has felt that they hurt more than they did prior to the Tdap vaccine.

Id. The musculoskeletal examination revealed good range of motion in all major joints, no joint swelling or redness, normal strength, and mild bony hypertrophy. Id. at 2. Dr. Said noted that Petitioner's joint pain "may represent serum sickness after she had the T[d]ap vaccine," which had improved, but symptoms could be masked by her current course of steroids. Id. at 3. Dr. Said prescribed pain medication and ordered additional tests. Id.

On September 30, 2014, Petitioner told Dr. Hashmi that she ordered low-dose Naltrexone[17] through an online pharmacy and had been using it for treatment of her hand pain. Pet. Ex. 16 at 66. Dr. Hashmi indicated that he was not comfortable prescribing this medication for long-term off-label use. Id. at 67. On examination, Dr. Hashmi observed minimal edema in the small joints of Petitioner's hands. Id. at 66. Magnetic resonance imaging ("MRI") of the brain and spine were ordered and conducted on October 8, 2014. Id. at 67. The results were unremarkable. Pet. Ex. 10 at 2-10.

Petitioner returned to Dr. Said for a rheumatology follow-up on October 23, 2014. Pet. Ex. 7 at 7. She was taking low-dose Naltrexone and Aleve. Id. She was not taking steroids. Id. Petitioner reported she was feeling better overall but was still having pain in some of her finger joints as well as paresthesias in her hands and feet. Id. Examination revealed no active swelling

[16] Many studies have shown the presence of anti-Sm antibodies along with other manifestations can be "predictive for an evolution to [systemic lupus erythematosus]." Resp. Ex. A-1 at 2.

[17] Naltrexone is "a synthetic congener of oxymorphone" that "acts as an opioid antagonist." Naltrexone Hydrochloride, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=33113 (last visited Oct. 5, 2022). Oxymorphone is "used as an analgesic for relief of moderate to severe pain." Oxymorphone Hydrochloride, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=36220 (last visited Oct. 5, 2022).

or synovitis.[18] Id. Dr. Said's diagnoses were positive RNP antibody and arthralgia. Id. at 8. She advised Petitioner to follow-up in one month. Id.

Six days later, on October 29, 2014, Petitioner presented to a different rheumatologist, Jonathan D. Reyes, M.D., of Denton Rheumatology. Pet. Ex. 3 at 8. Physical examination revealed decreased muscle strength in Petitioner's shoulders and hip flexors, no swollen joints, and 12 tender points. Id. at 10. The "rheumatologic review" was positive for dry eyes, dry mouth, oral ulcers, arthralgias, leukopenia/eosinophilia, ANA, anti-RNP, Raynaud's, and esophageal dysmotility problems. Id. at 9. Under assessment, Dr. Reyes stated,

> The patient is presenting with abnormal labs (ANA+, anti-RNP+) associated with joint pains. Joint pains got more pronounced after a recent immunization. We will have to consider and rule out [CTDs] at this time due to her positive ANA and the associated symptoms (joint pains, mouth sores, leucopenia, dry eyes, dry mouth).

Id. at 11. Hand and feet X-rays were obtained on October 29, 2014. Pet. Ex. 8 at 2-7. According to the radiologist, the results were unremarkable. Id. Dr. Reyes, however, noted the findings were suggestive of early osteoarthritis ("OA"). Pet. Ex. 3 at 6.

On November 19, 2014, Petitioner presented for a follow-up visit with Dr. Reyes. Pet. Ex. 3 at 6-7. The history noted that Petitioner was "doing just about the same with joint pains over her hands and feet." Id. at 6. "[H]er labs showed a positive ANA and anti-RNP . . . otherwise the rest of the serologic markers [were] negative." Id. Dr. Reyes noted further that Petitioner was not anemic or leukopenic, and her eosinophils were slightly elevated at seven. Id. Petitioner reported morning stiffness lasting "about half an hour." Id. Physical examination revealed mild tenderness over some of the finger joints in both hands, as well as metatarsophalangeal ("MTP") joints in both feet. Id. Dr. Reyes' diagnoses were UCTD[19] and OA of the hands and feet. Id. He noted that Petitioner "ha[d] some signs and symptoms suggestive of [CTD] but she [did] not have enough criteria to diagnose [systemic lupus erythematosus] or [other] [CTDs] at this time." Id. at 6-7. Given Petitioner's positive ANA and anti-RNP, Dr. Reyes decided to "approach this [as] a case of [MCTD]" and observe Petitioner for the development of any specific disease in the future. Id. at 7. He prescribed Mobic and

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[18] Synovitis is "inflammation of a synovial membrane" that "is usually painful, particularly on motion, and is characterized by a fluctuating swelling due to effusion within a synovial sac." Synovitis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=48576 (last visited Oct. 5, 2022). Synovial membrane 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." Membrana Synovialis Capsulae Articularis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=88558 (last visited Oct. 5, 2022).

[19] The diagnosis code was "unspecified diffuse [CTD]" Pet. Ex. 3 at 6. For clarity, the undersigned will refer to this diagnosis as UCTD.

instructed Petitioner to stay active, perform muscle strengthening exercises, and return to the clinic in six months. Id.

On May 20, 2015, Petitioner presented for a six-month follow-up visit with Dr. Reyes. Pet. Ex. 3 at 2-3. Petitioner reported Mobic gave her palpitations, so she switched to Aleve as needed. Id. at 2. Petitioner still complained of joint pains in hands and feet. Id. She also reported a burning sensation over her upper arms and thighs as well as fluctuating energy levels. Id. Rheumatologic review was positive for oral sores, arthralgias, dry eyes, and Raynaud's in feet more than hands. Id. Physical examination revealed mild tenderness over some joints of both hands and both feet, as well as 4/5 strength in the hips. Id. Dr. Reyes' diagnoses were UCTD, Raynaud's syndrome, and generalized muscle weakness. Id. at 2-3. Petitioner was prescribed Tramadol and instructed to follow up in six months. Id. at 3.

Petitioner followed up with Dr. Dalton on July 13, 2015. Pet. Ex. 6 at 59. Dr. Dalton's history noted that Petitioner was diagnosed with MCTD by a rheumatologist and that "[a]ll of her symptoms of this started with a DTaP shot." Id. On July 27, 2015, Petitioner presented to the Amarillo Veterans Affairs Health Care System ("VA") to establish care. Pet. Ex. 19 at 70-71. She relayed her history of MCTD. Id. at 71. Physical examination showed "some tenderness over [MCPs] and [MTPs]." Id. at 72. Gabapentin was prescribed for myalgia, and the plan was to obtain more labs, review past records, and refer Petitioner to the VA's rheumatologist. Id. at 73.

About four months later, on November 18, 2015, Petitioner followed up with Dr. Reyes. Pet. Ex. 3 at 4. Petitioner stated that her joint pain continued, she felt more tired, she had a burning pain over her thighs when she got up from a seated position, and she noticed nighttime fever and sweats. Id. Petitioner also relayed her belief that her Tdap vaccination in August 2014 "brought about or precipitated the expression/exacerbation of her symptoms." Id. Physical examination showed mild tenderness over some joints of both hands and both feet, but no swollen, red, or hot joints. Id. Strength in Petitioner's hips and shoulders was mildly decreased (4+/5). Id.

On February 24, 2016, Petitioner presented for her first evaluation at the VA rheumatology clinic with Dr. Carlos A. Plata. Pet. Ex. 19 at 65. Dr. Plata took the following history:

> Patient indicates that while she was in the military she was diagnosed with [CFS] and at that time, workup was done and she was told [she had] high titers of [EBV]. She since then has had some problems with chronic fatigue and general malaise. She had a workup redone a few years ago by a rheumatologist in Denton where she lives and was found to have a positive ANA and a positive rheumatoid factor anti RNP. With that she was diagnosed possible tonic-clonic seizure disorder[20] however just anti-inflammatories were tried and since then she has had episodes of general malaise and joint swelling affecting mostly the hands and

[20] The reference to a seizure disorder was an error. A later addendum clarified that Petitioner does not have a seizure disorder, but an autoimmune disorder. Pet. Ex. 19 at 67.

> feet. She has ha[d] fatigue also and morning stiffness lasting an hour or 2. She has variable Raynaud phenomenon that could be pretty significant in the winter . . . otherwise no major skin issues. She does have some dryness in eyes and mouth that is mild not very significant never had any swelling, never had any photosensitivity.

Id. Petitioner reported that her past medical history "[i]nclude[d] flare of her disease after a tetanus shot." Id. Physical examination showed minimal chronic synovitis in some MCPs of both hands and minimal tenderness in the MTPs. Id. at 66. Dr. Plata thought Petitioner had an autoimmune disease, but he did not think that the differential diagnosis would "make a big difference" in her care. Id. at 66-67. The plan was for Petitioner to start on Plaquenil and use non-steroidal anti-inflammatory drugs ("NSAIDs") and tramadol for flare-ups. Id. at 67.

Over the next year, Petitioner was followed by Dr. Reyes (Pet. Ex. 20 at 3-6), practitioners at CareHere Clinic (Pet. Ex. 16 at 73-80), and practitioners at the VA (Pet. Ex. 19 at 58-65). On November 16, 2016, Dr. Reyes noted that Petitioner felt the low-dose Naltrexone and a gluten-free/grain-free diet were helping to control her symptoms. Pet. Ex. 20 at 3. Her joint pains were "not completely resolved but [were] manageable." Id. Petitioner complained of feeling feverish at times, occasional pain over hands, feet, and upper back, and recent onset of achiness and stiffness in upper arms and thighs. Id. Dr. Reyes noted that these symptoms "make[] one think of the possibility of PMR (Polymyalgia Rheumatica)." Id. at 3-4. Nevertheless, Dr. Reyes concluded that Petitioner had "already completed 2 years of follow up for the positive ANA and thus far, there has not been any apparent development of specific [CTD]. I think that we can already stop monitoring her for possible CTD's at this time, but this is not to say that she can never ever develop any CTD in the future." Id. at 4.

In 2016, genetic testing revealed that Petitioner had an MTHFR polymorphism,[21] and treatment with folic acid was initiated. Pet. Ex. 16 at 76-78.

On July 22, 2016, the VA issued a determination that Petitioner was 100% disabled. Pet. Ex. 4 at 1, 5. The VA "assigned a 100 percent evaluation for [Petitioner's] [MCTD] with positive ANA/RNP and residuals of [EBV] based on: Acute, with frequent exacerbations, producing severe impairment of health. This is the highest schedular evaluation allowed under the law for systemic lupus erythematosus." Id.

On December 8, 2016, a nurse practitioner at CareHere Clinic noted that in addition to the folic acid preparation Enlyte, Petitioner's medications included Naltrexone, estrogen,

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[21] For an explanation of the methylenetetrahydrofolate reductase ("MTHFR") gene and related variants, see MTHFR Gene, Folic Acid, and Preventing Neural Tube Defects, Ctrs. for Disease Control & Prevention, https://www.cdc.gov/ncbddd/folicacid/mthfr-gene-and-folic-acid.html (last reviewed June 15, 2022). A genetic polymorphism is "the long-term occurrence in a population of multiple alternative alleles at a locus, with the rarest ones being at a frequency greater than could be maintained by recurrent mutation alone." Genetic Polymorphism, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=99319 (last visited Oct. 5, 2022).

progesterone, tramadol, NSAIDs, and natural herbal medicines. Pet. Ex. 16 at 78. The history of allergies noted in this record included "[Tdap] vaccine - serum sickness reaction." Id. Petitioner denied headaches, muscle aches, or weakness at that office visit. Id.

In February 2017, Petitioner began receiving treatment from a holistic practitioner, Jerald L. Tennant, M.D., M.D. (H), PScD (doctor of pastoral medicine) through the Tennant Institute of Integrative Medicine. See Pet. Ex. 14 at 17-29; Pet. Ex. 15; Pet. Ex. 18.

On March 15, 2017, Petitioner saw Dr. Plata in rheumatology for a follow-up and reported that she did not start the Plaquenil after her last visit. Pet. Ex. 19 at 57. Petitioner was reporting more frequent arthralgia, general malaise, and worsening fatigue. Id. Physical examination revealed "minimal chronic synovitis in MCPs of both hands, with mild tenderness especially on the right side," and "straight dependent edema." Id. Dr. Plata noted that Petitioner was affected by "a mild disease" with "constitutional symptoms that are mild, but are more annoying at this time." Id. at 58. Dr. Plata recommended that Petitioner try Plaquenil, and Petitioner agreed. Id. By September 19, 2017, six months later, Petitioner's achiness reportedly improved on the medication. Id. at 49.

B. Petitioner's Affidavit

Petitioner averred that prior to the vaccination at issue here, she "ha[d] an autoimmune condition, diagnosed approximately [one] month prior to the vaccine." Pet. Ex. 12 at ¶ 1. "The autoimmune condition was discovered by . . . a positive RNP antibody, as well as a positive ANA." Id. Petitioner related her positive ANA to her time "in the U.S. Marine Corps and [her] diagnosis of [CFS], with consequent highly positive antibodies for [EBV] in the 1980s." Id. Upon exiting the Marine Corps, Petitioner stated her CFS lingered; she continued to have a positive ANA, but she had no joint or muscle pain. Id. at ¶¶ 1-2.

Within hours of receiving the Tdap vaccine on August 8, 2014, Petitioner felt feverish and achy. Pet. Ex. 12 at ¶ 5. The following date, Petitioner was exhausted and had a fever. Id. Within a few days, Petitioner collapsed while standing due to "unbearable pain in [her] joints, [her] knees, [her] back, and [her] hands and feet. [She] could barely walk and suffered debilitating exhaustion." Id. Petitioner returned to CareHere Clinic on August 20 and September 9, complaining of joint pain, mostly in her hands and feet. Id. Petitioner continued to see doctors, including two rheumatologists, for her painful and swollen joints, as well as muscle pain and muscle spasms. Id. at ¶ 6. Petitioner noted rheumatologist Dr. Said diagnosed her with "'serum sickness' from the Vaccine and [MCTD]." Id. Petitioner stated Dr. Reyes, a rheumatologist, "told [her] that the Vaccine was the precipitating factor that triggered [her] condition." Id. "With a severely restricted diet and supplements, [she] ha[s] managed the pain somewhat better." Id. at ¶ 8.

As of the date Petitioner executed the affidavit, April 27, 2017, Petitioner averred that "[she] continue[s] to suffer joint and muscle pain and spasms which wax and wane and flare unexpectedly." Pet. Ex. 12 at ¶ 9. She also stated that she "can hardly get out of bed in the morning for the stiffness in [her] legs and feet." Id. "[Her] hands and feet are now disfigured

and remain inflamed and painful." Id. In an attempt to reduce the inflammation, Petitioner eats mostly vegetables. Id.

C. Expert Reports[22]

1. Petitioner – Dr. Joseph A. Bellanti[23]

a. Background and Qualifications

Dr. Bellanti is board certified in pediatrics and allergy and immunology. Pet. Ex. 49 at 4. He received his M.D. from the University of Buffalo in 1959, after which he completed an internship at Millard Fillmore Hospital in Buffalo, New York and a pediatric residency at the Children's Hospital of Buffalo. Id. at 3. Dr. Bellanti completed a special NIH training in Immunology and was a Research Virologist at Walter Reed Army Institute of Research. Id. He currently works as a Professor of Pediatrics and Microbiology-Immunology at Georgetown University School of Medicine, and serves as Director of the International Center for Interdisciplinary Studies of Immunology at Georgetown University and Director of the Division of Immunology and Virology in the Department of Laboratory Medicine at Georgetown University Hospital. Id. at 1. Dr. Bellanti also holds pediatric staff positions at various hospitals, including Georgetown University Hospital, Children's Hospital National Medical Center, Arlington Hospital, and INOVA Fairfax Hospital. Id. He has participated in numerous scientific and professional societies and committees, and has authored or co-authored over 450 publications. Id. at 5-7, 12-51.

b. Opinion

i. Diagnosis

Dr. Bellanti conceded that due to Petitioner's clinical course, symptoms, findings, and treatments described in her records, it is difficult to arrive at "a definitive diagnosis." Pet. Ex. 48 at 3. He opined that UCTD, as shown in an illustration in Dr. Reyes' medical record,[24] is the diagnosis that "probably comes the closest to describing [Petitioner's] condition."[25] Id. Other diagnoses that have been used to describe Petitioner's illness include CTD, MCTD, CFS, and "some kind of immunodeficiency." Pet. Ex. 63 at 14. He added that Petitioner's "condition is

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[22] Because Petitioner does not rely on the expert report from Dr. Mikovits and Dr. Ruscetti, the undersigned will not address their report and opinions. See Tr. 5-6; Pet. Prehearing Memo.; Pet. Mot.; Pet. Reply; Pet. Witness & Exhibit List, filed Apr. 28, 2020, at 2 n.3 (ECF No. 74).

[23] Dr. Bellanti submitted three expert reports. Pet. Exs. 48, 63, 65.

[24] See Pet. Ex. 3 at 1.

[25] Although Dr. Bellanti referenced an illustration of UCTD in Dr. Reyes' records, Dr. Reyes' "working diagnosis [for Petitioner was] MCTD (ANA positive, anti-RNP positive) and [o]steoarthritis of the hands an[d] feet." Pet. Ex. 3 at 1-2.

always associated with a longstanding positive ANA[] and a positive EBV," and "does not fit neatly into any category." Id. He opined that "[r]egardless of where on th[e] [CTD] spectrum [Petitioner] falls, they are all autoimmune conditions." Id. at 15.

Regardless of her specific diagnosis, Dr. Bellanti asserted that Petitioner's "illness dramatically worsened," and she developed new symptoms, after her Tdap vaccination. Pet. Ex. 48 at 3.

ii. Loving Factor Four/Althen Prong One

Regarding causation, Dr. Bellanti opined that Petitioner's Tdap vaccine caused reactivation of latent EBV, which caused a dramatic worsening of a pre-existing autoimmune/auto-inflammatory disease. Pet. Ex. 63 at 14. He stated that "[t]here are several well-documented theories about how the [Tdap] vaccination could have triggered the activation of the EBV." Pet. Ex. 48 at 4. He asserted that the latent EBV infection "in the healthy individual is maintained in check by the CD8 T lymphocytes. It is now well known that several environmental factors that depress the function of these viral-restricting T cells can activate the clinically silent latent infection, causing reactivation of virus with more destruction of the target cells and exacerbation of clinical symptoms." Id. at 5. He opined that environmental stimuli include "stress, fever, infection[,] or vaccination." Id.

Dr. Bellanti discussed three mechanisms relevant to latent EBV infections and reactivation. First, "[t]he central mechanism[] controlling EBV reactivation [is] epigenetic." Pet. Ex. 48 at 5. He defined this as "changes in the expression of genes, without a change in the nucleotide sequence of the virus." Id. Dr. Bellanti added that while "much is known about the molecular pathways involved in viral reactivation[], what triggers reactivation *in vivo* is not known precisely. The presumption is that it occurs when latently infected B cells respond to unrelated infections, because B-cell receptor stimulation triggers reactivation in B-cell lines." Pet. Ex. 63 at 17 (quoting Pet. Ex. 55 at 3).

He cited a comprehensive article by Odumade et al., which addressed primary infection, EBV latency, and reactivation. Pet. Ex. 55. Odumade et al. explained that EBV, a human herpesvirus (HHV-4), is thought to cause an initial infection in the tonsils. Id. at 2. Lymphocytes and epithelia cells act as host cells. Id. EBV attaches to B cells, and ultimately the genome of the virus "is transported to the nucleus, where it is replicated by DNA polymerases." Id. The authors defined latency as "the state of persistent viral infection without active viral production. EBV persists mostly in the memory B-cell compartment . . . . Currently, it is thought that one in a million B cells carry the EBV genome in an individual after recovery from acute infection." Id. "Latently infected B cells can occasionally be stimulated to reactivate EBV. This produces virus that can reinfect new B cells and epithelial cells, becoming a source of viral transmission." Id. at 3. Odumade et al. explained that "what triggers reactivation [] is not known precisely," but that "[t]he presumption is that it occurs when latently infected B cells respond to unrelated infections." Id.

Second, Dr. Bellanti stated that "dysregulation of microglia, dendritic cells, B-cells (antigen presenting cells) by the specific antigens or excipients in the vaccine preparation can []

be responsible for EBV reactivation by altering DNA, leading to CD8+ T cell activation." Pet. Ex. 48 at 5. Similarly, he opined that the "dysregulation of microglia, dendritic cells, B-Cells (antigen presenting cells) by aluminum and endotoxin in the vaccine can also allow the EBV to reactivate by altering DNA, leading to CD8+ T cell activation. These cells are critical to clearing acute EBV." Pet. Ex. 63 at 16. However, Dr. Bellanti failed to explain how the Tdap vaccine alters DNA, or dysregulates cells to cause "chronic expression of inflammatory cytokines," or otherwise cause reactivation of EBV. Pet. Ex. 48 at 5. Nor did he explain how aluminum and endotoxin in the vaccine lead to EBV reactivation.

In support of this second mechanism, Dr. Bellanti cited Eligio et al.,[26] who stated "CD8+ T cells are essential for recovery from [infectious mononucleosis]," the acute illness caused by EBV. Pet. Ex. 52 at 4. But the authors did not discuss vaccines, or suggest that vaccines play any role in reactivation of EBV. They also did not discuss aluminum or endotoxin in vaccines.

Eligio et al. also stated that CD8+ T cells are especially important in the context of "primary EBV infection in immunocompromised individuals who are unable to mount the appropriate response and who usually die of fulminating [infectious mononucleosis]-like syndrome within weeks of acquiring EBV." Pet. Ex. 52 at 4. Dr. Bellanti stated that "[Petitioner] was unable to 'clear' the virus due to her immunodeficiency[,] . . . [y]et her condition remained relatively stable" until her vaccination. Pet. Ex. 63 at 16. Leaving aside the questions of whether Petitioner was immunocompromised, had an immunodeficiency order, or was able to "clear" her body of the EBV virus after she was initially infected, the Eligio et al. paper does not speak to EBV reactivation following vaccination.

Third, Dr. Bellanti proposed that "[m]olecular mimicry can be involved at both the nucleic acid (altering regulatory RNA) or at the protein level due to cross reactivity among the various antigens in the vaccine." Pet. Ex. 48 at 5. He explained that vaccines contain viral compounds and other excipients that stimulate an immune response. Pet. Ex. 63 at 17. If the antigens contained in the vaccine share homology with antigens in the host, "then the immune response will be directed at both the injected antigens and host antigens, leading to an autoimmune response." Id. "Molecular mimicry can be involved at both the nucleic acid (altering regulatory RNA) or at the protein level due to cross reactivity among the various antigens in the Tdap vaccine, [and] the more than 100 [EBV] antigens and human cells." Id. at 17-18.

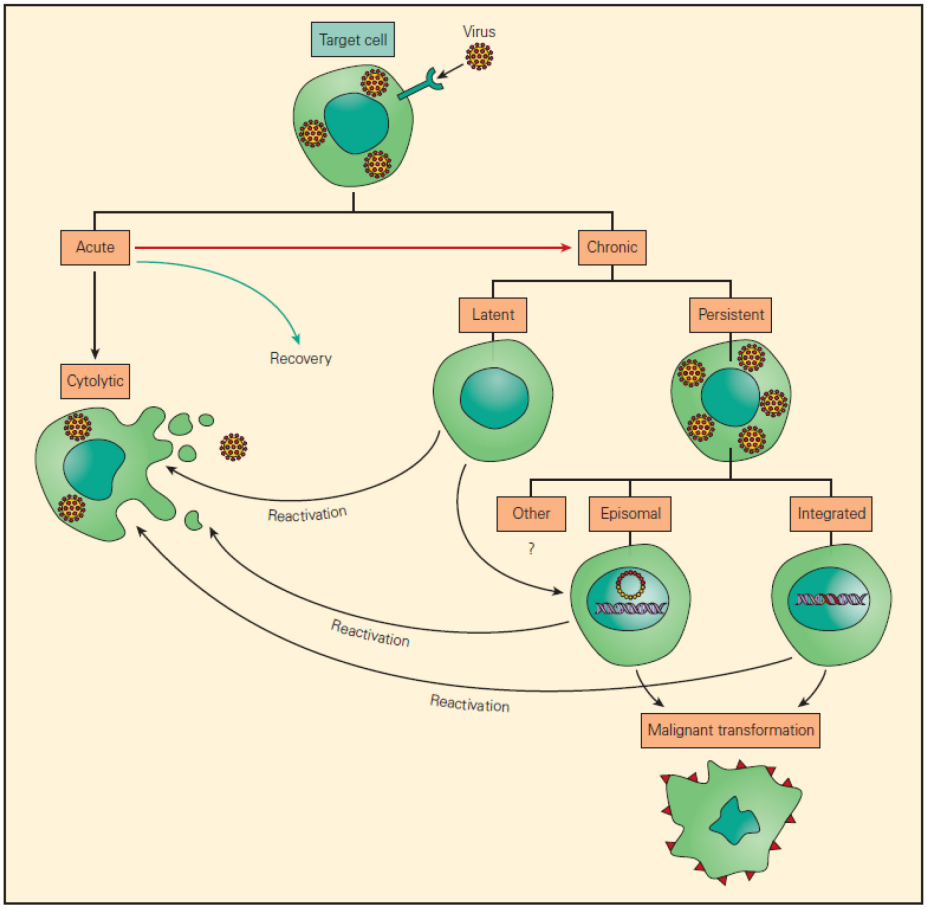
He cited Kanduc and Shoenfeld[27] in support of this mechanism, stating that they "detail the mimicry that occurs with cross reactivity of hundreds of peptide and nuclear acid sequences expressed from [r]eactivated EBV and the human genome." Pet. Ex. 48 at 5. The Kanduc and Shoenfeld article, however, does not speak to EBV reactivation at all. The question addressed was, "given the massive peptide overlap that characterizes the protein world, [are there] peptide

[26] Pizzigallo Eligio et al., EBV Chronic Infections, 2 Mediterranean J. Hematology & Infectious Diseases e2010022 (2010).

[27] Darja Kanduc & Yehuda Shoenfeld, Inter-Pathogen Peptide Sharing and the Original Antigenic Sin: Solving a Pardox, 8 Open Immunology J. 16 (2018).

commonalities among viruses, bacteria[,] and protozoans that might confound, intensify[,] or weaken the human immune responses that follow infection [and/or] active immunization?" Pet. Ex. 53 at 2. To study the question, they used HPV16 infections/vaccinations as a model to explore the "immunologic impact" that prior infections/vaccinations might have had on "human anti-HPV16 immune responses." Id. The central question was whether certain viruses (including EBV) and bacteria which share epitopes, creating the potential for cross-reactivity, play a role in a mechanism whereby "different infections over time . . . imprint the host immunological memory," leading to an enhanced or inappropriate immune response. Id. at 7. The research, however, did not address EBV reactivation, or how vaccines generally, or the Tdap vaccine specifically, can cause EBV reactivation. There was no suggestion that the Tdap vaccine, through the mechanism of molecular mimicry, or any other mechanism, could reactivate a latent EBV infection.

After discussing the three mechanisms, Dr. Bellanti cited an illustration from his textbook entitled Immunology[28] to discuss how chronic viral infections, including one that is latent, may be reactivated to cause a "cytolytic infection with cell destruction" or "malignant transformation." Pet. Ex. 48 at 6 (citing Pet. Ex. 51 at 5 fig.13-4).



[28] Joseph A. Bellanti & Barry T. Rouse, Mechanisms of Immunity to Viral Disease, in Immunology IV: Clinical Applications in Health and Disease 459 (Bellanti et al. eds., 4th ed. 2012).

Pet. Ex. 51 at 5 fig.13-4. The illustration, however, does not explain how vaccines, or the Tdap vaccine, can cause reactivation of the EBV infection.

Lastly, Dr. Bellanti cited a comprehensive literature review article about CFS authored by Noor et al. Pet. Ex. 66. There, the authors acknowledged that CFS was initially associated with EBV infections, but that "it was later determined that it was not always preceded by EBV infection." Id. at 1. The authors stated that "[p]ossible triggering events, such as infections followed by an immune dysregulation resulting have been proposed." Id. But they concluded that the "cause of CFS remains unknown." Id. at 2. The articles did not speak to a mechanism whereby EBV is reactivated, or discuss any role played by vaccines in EBV reactivation.

Throughout his expert reports, Dr. Bellanti maintained that the literature "shows what [the] triggers [for EBV reactivation] are, and they include several excitants, like stress, fever, infection[,] or vaccination." Pet. Ex. 63 at 21. He cited two sources in support of the proposition that vaccination is a trigger for EBV reactivation. Id. The first is a paper by Kempkes and Robertson. Pet. Ex. 54. However, it does not mention vaccines, or suggest that vaccines play any role in triggering reactivation. See id. The second article is by Scott,[29] and it focused on EBV's oncogenic activity. Pet. Ex. 57. Scott does not discuss vaccines or reactivation or their relationship relative to CTDs or CFS. See id.

iii. Loving Factor Five/Althen Prong Two

Dr. Bellanti opined that the Tdap vaccination caused reactivation of Petitioner's EBV infection, which lead to a worsening of her underlying "autoimmune condition ([MCTD]/[CFS])." Pet. Ex. 63 at 23. He explained that Petitioner previously had an underlying EBV infection, which was latent for 30 years, "during which there was a controlled mild presentation of the autoimmune condition." Id. She received the Tdap vaccination on August 8, 2014, which Dr. Bellanti asserted was followed by a "serum sickness like reaction [that] overwhelmed the balance of her immune system and thus [caused] the reactivated EBV." Id. The consequence of EBV reactivation was "significant joint and muscle pain" and an "increase in her disability rating from 10% to 100%." Id. He asserted that the Tdap vaccination, "likely through the initial serum sickness like reaction[], [] ultimately exacerbated the underlying autoimmune condition that had been originally caused by [] EBV." Id. at 24.

In his Factor Five/Prong Two opinions set forth in his second report, Dr. Bellanti mentioned Petitioner developed a serum sickness-like reaction, which exacerbated her underlying autoimmune condition. Pet. Ex. 63 at 22-23. He did not explain what a serum sickness-like reaction is, or how it could have played a role in causing an exacerbation of Petitioner's underlying illness. Also, he did not explain how his proposed mechanisms caused a serum sickness-like reaction, or the relationship between his mechanisms and such a reaction. Further, he did not offer any medical literature or other supportive evidence on this point.

[29] Rona S. Scott, Epstein-Barr Virus: A Master Epigenetic Manipulator, 26 Current Op. Virology 74 (2017).

Dr. Bellanti made several assertions about why he believed Petitioner's Tdap vaccination caused Petitioner's EBV reactivation and the resulting worsening of her underlying condition. He first asserted that Petitioner's underlying condition had been stable for 30 years because of a "careful balance [] between the virus and the immune system." Pet. Ex. 63 at 18 (quoting Pet. Ex. 55 at 6). He further asserted that Petitioner "had not demonstrated any flares or changes of note in her condition during that [30-year time period]." Id. at 24. However, a review of Petitioner's medical records belies the notion that her underlying condition was stable. For example on July 18, 2013, Petitioner presented to Dr. Rea, complaining of a thirty-year history of fatigue and chronic infections. Pet. Ex. 5 at 28. And on September 16, 2014, Petitioner saw Dr. Said and reported "intermittent flares of her EBV" since her EBV infection "about 30 years ago." Pet. Ex. 7 at 1.

The next assertion Dr. Bellanti made regarding Factor Five/Prong Two is that other than the vaccination at issue, there were no other "epigenetic or environmental factors" experienced by Petitioner prior to the worsening of her condition. Pet. Ex. 63 at 18. He noted "[a] review of her medical records indicate[d] no undue or unusual stress, there was no fever, no infection, no other unusual biological or chemical agent, and no other significant factor present other than her vaccination." Id. (emphasis omitted). However, in July 2013, Petitioner complained of chronic infections. Pet. Ex. 5 at 28. Dr. Rea ordered the treatment of "autogenous vaccine" for Petitioner. Id. at 18; see also Pet. Ex. 6 at 39. On October 25, 2013, Petitioner saw Dr. Dalton, who noted that Petitioner "present[ed] with [g]etting infections too easily and then needs antibiotics and then antifungals." Pet. Ex. 6 at 46. Dr. Dalton's diagnoses included reactions to food, bacterial vaginitis, menopause, and postmenopausal hormone replacement. Id. at 47.

iv. Loving Factor Six/Althen Prong Three

Dr. Bellanti stated Petitioner received the Tdap vaccination on August 8, 2014, and the next day, she developed severe swelling of her joints, with redness and warmth. Pet. Ex. 63 at 24. Petitioner also reported fever, felt ill, and required a Medrol Dosepak for improvement. Id. Dr. Bellanti opined that "[t]his timing is appropriate for the initial immune-mediated response and the subsequent exacerbation of her condition." Id. at 24-25.

According to Dr. Bellanti, this timeframe of onset, described as one day, is supported by the medical literature. Pet. Ex. 63 at 25. He also stated that "several of [Petitioner's] treating doctors relate the timing of her Tdap vaccination to her significantly aggravated condition." Id. For support, he cited Dr. Dalton's statement that "[a]ll hell broke loose with a tetanus shot." Id. (quoting Pet. Ex. 6 at 7).

Regarding the mechanism by which the Tdap vaccine reactivated Petitioner's EBV, Dr. Bellanti relied upon on molecular mimicry. The articles cited by Petitioner, however, do not speak to the appropriate timeframe within which molecular mimicry could cause EBV reactivation post-vaccination.

2. Respondent – Dr. Erin M. Wilfong[30]

a. Background and Qualifications

Dr. Wilfong is board certified in internal medicine and rheumatology. Resp. Ex. A at 1; Resp. Ex. B at 2. After receiving her M.D. and Ph.D. in Chemistry from Duke University, she completed an internal medicine residency at Johns Hopkins Hospital, a rheumatology fellowship at the University of California, San Francisco, and a pulmonary & critical care fellowship at Vanderbilt University. Resp. Ex. A at 1; Resp. Ex. B at 1. Dr. Wilfong has experience working with patients with CTD. Resp. Ex. A at 1. She has won numerous awards, completed various research projects, and co-authored several publications. Resp. Ex. B at 3-5.

b. Opinion

i. Diagnosis

Dr. Wilfong opined as to each of Petitioner's suggested diagnoses in turn. First, however, she described the umbrella term, CTDs, as the family of "systemic rheumatic diseases associated with a positive ANA." Resp. Ex. A at 3. These include "systemic lupus erythematosus, [MCTD], Sjogren's syndrome, [] systemic sclerosis, as well as [UCTD]." Resp. Ex. A at 3. Those who have UCTD "have some features of autoimmunity, but do not meet diagnostic/classification criteria for a defined [CTD]." Id. In contrast, UCTD is a "systemic autoimmune condition[] characterized by a mild clinical profile and a simplified autoimmune repertoire." Id. (quoting Resp. Ex. A-1 at 3). "Only a minority of patients with UCTD evolve to develop a full [CTD]." Id.

MCTD is defined by Dr. Wilfong as "a distinct condition with features of systemic lupus erythematosus, inflammatory myositis, and systemic sclerosis," and its hallmark is "the presence of anti-U1RNP autoantibodies and anti-nuclear antibodies." Resp. Ex. A at 3. In fact, U1RNP antibodies are pathognomonic for MCTD. Id. at 4. Patients with this illness often have "Raynaud's phenomenon, sclerodactyly (skin tightening), arthritis, and esophageal dysmotility." Id.

Dr. Wilfong opined that Petitioner "did not develop MCTD after receiving the Tdap vaccine." Resp. Ex. A at 4. In support of her opinion, she cited Dr. Reyes' November 19, 2014 note, which stated,

> The patient does have some signs and symptoms suggestive of [CTD,] but she does not have enough criteria to diagnose [systemic lupus erythematosus] or othe[r] [CTDs] at this time. [H]er [ANA] and anti-RNP are positive and thus we will treat and approach this [a]s a case of [MCTD], and observe her over time to see if she will develop any specific disease in the future.

[30] Dr. Wilfong submitted two expert reports. Resp. Exs. A, E.

Pet. Ex. 3 at 6-7. Thus, Dr. Wilfong believed that it was clear that Petitioner did not meet the criteria for MCTD at this visit in November 2014, and that Dr. Reyes planned to monitor her for a two-year period. Resp. Ex. A at 2, 5. Further, during this period of monitoring, Dr. Reyes used the diagnostic code for UCTD. Id. at 2.

Two years later, on November 16, 2016, at the completion of the monitoring period, Dr. Reyes noted that Petitioner had "completed 2 years of follow up for the positive ANA and thus far, there has not been any apparent development of specific [CTD]." Pet. Ex. 20 at 4. Therefore, Dr. Wilfong concluded that Petitioner's vaccination did not cause her to develop MCTD. Resp. Ex. A at 5.

Similarly, Dr. Wilfong explained that Dr. Plata did not diagnosis Petitioner with MCTD. Resp. Ex. A at 5. Instead, Dr. Plata used the former name for CTD, "Collagen Vascular Disease," as Petitioner's diagnosis. Id.

In addition to the fact that Petitioner's treating physicians did not diagnose her with MCTD, Dr. Wilfong observed that Petitioner had a positive RNP on August 8, 2014, the date of vaccination. Resp. Ex. A at 2. Therefore, Petitioner's abnormal lab value was not due to her vaccination. Id. Also, she observed that Petitioner did not have a "persistently positive RNP antibody," which is a requirement for the diagnosis of MCTD.[31] Id. at 5, 13.

A summary of Petitioner's RNP lab results are shown below, in a summary prepared by Dr. Wilfong:

Table 1. Summary of RNP test results

Date	Reference Lab	Result	Normal Range	Exhibit/Page
8/8/2014	Not reported*	4.6	<0.9	Ex. 13, page 7/102
10/23/2014	LabCorp	4.1	<0.9	Ex. 7, page 6/11
10/29/2014	ClearPoint/Med Fusion	Positive	Negative	Ex. 3, page 33/65
10/29/2014	Exagen Diagnostics	0.7	<7	Ex. 3, page 31/65
5/20/2015	Exagen Diagnostics	0.9	<7	Ex. 3, page 23/65
11/19/2015	Exagen Diagnostics	0.7	<7	Ex, 3, page 14/65
7/25/2016	LabCorp	3.7	< 0.9	Ex. 1, page 33/120
11/19/2016	Exagen Diagnostics	2	<5	Ex. 20, page 26/39
2/24/2016	VA/Quest	<1	<5	Ex. 19, page 24/181

* Lab performed at Family Health Center. All other lab reports from this facility are from LabCorp.

[31] Dr. Wilfong observed that Petitioner's RNP antibody was "positive only when tested by LabCorp but not other reference labs." Resp. Ex. A at 5. She opined that "[n]egative results [from] numerous other reference labs both simultaneously and over many years indicates a false positive result on the LabCorp test." Id.

Resp. Ex. A at 2. As the chart shows, Petitioner had a positive RNP on the date of vaccination,. Id. Thereafter, the results were inconsistent. Id. Based on the fact that Petitioner did not have consistently positive RNP antibodies, Dr. Wilfong concluded that she did not meet the criteria for MCTD. Id. at 2, 5, 13.

The next relevant diagnosis is CFS,[32] which Dr. Wilfong explained is characterized by fatigue, post-exertional malaise, and unrefreshing sleep, along with cognitive impairment or orthostatic intolerance. Resp. Ex. A at 4. The cause is not known, but EBV and other viruses have been proposed as causes. Id. Other possible causes include "immune dysfunction, endocrine-metabolic dysfunction, depression, sleep disruption, and genetic(s)." Id. Dr. Wilfong opined that it was not clear whether Petitioner suffered from CFS because although her records documented chronic fatigue, they did not document "cognitive impairment, orthostatic intolerance, or non-restorative sleep." Id. at 5. She agreed, however, that Petitioner had been diagnosed with CFS. Id. Even if Petitioner met the criteria for CFS, and assuming she was properly diagnosed with CFS, Dr. Wilfong opined that there is no evidence that vaccination can cause CFS exacerbation. Id. at 4-5.

Lastly, Dr. Wilfong discussed serum sickness. Resp. Ex. A at 6. She agreed with Dr. Bellanti that "serum sickness is a type III hypersensitivity with complement system activation." Id. However, Dr. Wilfong explained that there is no evidence that Petitioner's complement system was activated as she did not have abnormally low C3 or C4 levels. Id. Thus, she opined that "[t]here is no documentation to support that the [P]etitioner had serum sickness after vaccination." Id.

In summary, Dr. Wilfong opined that Petitioner was diagnosed with UCTD, and that she never had MCTD. Nor was she diagnosed with MCTD. Resp. Ex. A at 4-5, 13. Further, she never had consistently elevated RNP antibodies, and her initial positive result was the date of vaccination, and thus not caused by vaccination. Id. at 2, 5. Petitioner also did not have serum sickness. Id. at 6, 13. Dr. Wilfong agreed that Petitioner had been diagnosed with CFS, although it was not clear whether she meet the criteria for the diagnosis. Id. at 5-6. Dr. Wilfong further opined that vaccination did not exacerbate Petitioner's underlying condition. Id. at 13.

ii. Loving Factor Four/Althen Prong One

Dr. Wilfong opined that there is "no evidence that the Tdap vaccine leads to reactivation of EBV." Resp. Ex. E at 3. She explained that the best example of EBV reactivation is in the context of organ transplantation, where patients are administered medication to induce "aggressive immunosuppression" to reduce the risk of organ rejection. Id. This degree of immunosuppression can contribute to EBV reactivation. Id. A significant complication of EBV

[32] Dr. Wilfong also referred to CFS as systemic exertional intolerance disease, or SEID. For simplicity and consistency, CFS will be used throughout this Decision.

reactivation in this setting is EBV-related lymphoma.[33] Id. "According to the United Network for Organ Sharing, 764,130 solid organ transplants have been performed since 1988," and in 2018, there were 36,519 performed. Id. at 3. As part of transplant protocol, the American Society of Transplant Surgeons, in 2009, recommended that patients receive the Tdap vaccine before and after organ transplantation. Id. Dr. Wilfong suggested that given this data, if the Tdap vaccine caused or contributed to EBV reactivation, there would likely be a published association between Tdap vaccination and EBV reactivation. Id. Dr. Wilfong used this lack of any such association to support her opinion that the Tdap vaccine does not cause EBV reactivation. Id.

Further, Dr. Wilfong asserted that the medical literature cited by Dr. Bellanti does not support the conclusion that Tdap vaccination causes EBV reactivation. Resp. Ex. E at 3-4. Dr. Wilfong summarized articles referenced by Dr. Bellanti, and explained why they fail to support his assertions. Id. at 4 (citing Pet. Exs. 50-56). For example, in Dr. Bellanti's book chapter, he wrote that herpes viral reactivation "is poorly understood, it seems to be related to conditions that depress cell-mediated immune function, such as stress or excessive exposure to sunlight, as well as underlying diseases, such as lymphoreticular malignancies, e.g. lymphoma." Id. (quoting Pet. Ex. 51 at 7). Dr. Wilfong noted that there is no discussion about how vaccinations cause reactivation of EBV. Id. As for the articles by Aligo et al. and Eligio et al., Dr. Wilfong noted there is no discussion of how vaccines lead to viral reactivation. Id. (citing Pet. Exs. 50, 52). Dr. Wilfong concluded that there is "no evidence supporting that the tetanus vaccine is a trigger for EBV reactivation." Id. at 5.

Lastly, Dr. Wilfong opined that "[t]here is no evidence . . . that vaccinations cause autoimmune disease flares." Resp. Ex. A at 11. Dr. Wilfong wrote "[v]accination of patients with autoimmune disease is safe and does not result in disease flare." Id. She cited a study from Mok et al.[34] of patients with systemic lupus erythematosus who received HPV vaccinations. Resp. Ex. A-22 at 1. The vaccinations did not cause any increase in illness compared with systemic lupus erythematosus patients who were not vaccinated. Id. The same was true in studies of systemic lupus erythematosus patients and rheumatoid arthritis patients who received the hepatitis B vaccine. Resp. Ex. A at 11 (citing Resp. Ex. A-23 at 1;[35] Resp. Ex. A-24 at 1).[36]

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[33] Lymphoma is "any neoplastic disorder of the lymphoid tissue." Lymphoma, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=29056 (last visited Oct. 5, 2022).

[34] Chi Chiu Mok et al., Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in Patients with Systemic Lupus Erythematosus: A Case-Control Study, 72 Annals Rheumatic Diseases 659 (2013).

[35] K.A.M. Kuruma et al., Safety and Efficacy of Hepatitis B Vaccine in Systemic Lupus Erythematosus, 16 Lupus 350 (2007).

[36] O. Elkayam et al., Safety and Efficacy of Vaccination Against Hepatitis B in Patients with Rheumatoid Arthritis, 61 Annals Rheumatic Diseases 623 (2002).

iii. Loving Factor Five/Althen Prong Two

Because "the mechanism by which EBV reactivates has yet to be elucidated," Dr. Wilfong stated that "it is exceedingly challenging to demonstrate the Tdap vaccine more likely than not led to an EBV reactivation." Resp. Ex. E at 3.

In addition to the fact that the mechanism of EBV reactivation is not known, there are a number of salient features of Petitioner's clinical course significant to Dr. Wilfong that weigh against vaccine causation. The first is that Petitioner was monitored by Dr. Reyes for two years after vaccination, and during this time she did not develop any specific CTD. Resp. Ex. A at 3. In fact, Dr. Reyes stopped monitoring Petitioner after that time. Id.

The second feature relates to the diagnostic studies of Petitioner's joints. In her petition, Petitioner described that "[h]er hands and feet are [] disfigured and remain inflamed and painful." Resp. Ex. A at 3 (quoting Petition at 3). However, diagnostic studies and pertinent medical records cited by Dr. Wilfong showed no significant findings. Id. Hand X-rays from July 27, 2015 show Petitioner had "[n]o fracture, dislocation[,] or subluxation" and "[n]o significant degenerative changes." Id. (quoting Pet. Ex. 19 at 7-8). Foot X-rays conducted the same day showed "[m]inimal degenerative changes without fracture, dislocation[,] or subluxation." Id. (quoting Pet. Ex. 19 at 9). Dr. Plata's records also did not document any deformity of the hands or feet. Id. Dr. Reyes records from November 2016 showed "[n]o tenderness or swelling over the wrists or MCPs. No tenderness over the knees, ankles[,] or toes. [P]rominent first MTPs but not tender." Id. (quoting Pet. Ex. 20 at 3).

Additional facts pertinent to Dr. Wilfong's opinions relate to the lack of evidence of immune dysregulation. Dr. Wilfong referenced Petitioner's visit to Dr. Rea on July 18, 2013, where labs were ordered due to the concern for immune dysregulation. Resp. Ex. E at 1 (citing Pet. Ex. 5 at 34). "[P]etitioner had immunoglobulin and lymphocyte subsets checked" and the results were "within normal limits." Id. (citing Pet. Ex. 5 at 20, 22).

Regarding Petitioner's EBV flares and/or reactivation, Dr. Rea's July 18, 2013 records documented that "[P]etitioner had an EBV titer of 2850. However, no date [was] associated with this titer, and the medical records [did] not include any associated lab work." Resp. Ex. E at 1 (internal citations omitted) (citing Pet. Ex. 5 at 29). At her rheumatology visit on September 16, 2014, Petitioner reported a history of having EBV 30 years before. Id. (citing Pet. Ex. 7 at 1). "[D]espite intermittent flares of her EBV[,] [she] ha[d] been fairly healthy and active and ha[d] only had mild joint pain." Id. at 1-2 (quoting Pet. Ex. 7 at 1). Dr. Wilfong stated the medical records did not include lab studies, or references to labs, evidencing that "[P]etitioner had an EBV infection or reactivation after 1992 to document any kind of 'flare.'" Id. at 2. Based on her VA records, Petitioner's "original diagnosis of EBV was made based upon an elevated EBV IgG with negative IgM in 1992. No elevated EBV viral load is included in the VA records." Id. (internal citations omitted) (citing Pet. Ex. 58 at 390).

Instead of vaccination, Dr. Wilfong suggested that a possible explanation[37] for "[P]etitioner's positive serologies and possible [UCTD] is . . . her chronic [EBV]." Resp. Ex. A at 12. Dr. Wilfong noted that chronic EBV is associated with autoimmune illness. Id. For example, the vast majority of systemic lupus erythematosus patients are EBV IgG positive when compared to healthy controls (99.5% versus 95%). Id. (citing Resp. Ex. A-30 at 5).[38] However, this is only a possibility, because there is no supportive evidence such as EBV titers, or other test results, to support a conclusion that Petitioner had chronic EBV. Id.; Resp. Ex. E at 3. Further, Dr. Wilfong observed there is no evidence of EBV reactivation after vaccination. Resp. Ex. E at 3. No studies were done that showed any increase in Petitioner's "EBV titers or viral load after vaccination to demonstrate EBV reactivation." Id.

iv. Loving Factor Six/Althen Prong Three

Dr. Wilfong did not specifically express an opinion as to the appropriateness of the temporal association between vaccination and alleged illness onset. The majority of her opinions addressed the different diagnoses at issue and the mechanism at play for each one. However, Dr. Wilfong opined that over the two-year period during which Dr. Reyes monitored Petitioner post-vaccination, Petitioner did not develop any specific CTD. Resp. Ex. A at 3.

3. Respondent – Dr. Evan J. Anderson[39]

a. Background and Qualifications

Dr. Anderson received his M.D. from the University of Chicago, after which he completed an internal medicine and pediatrics internship and residency, as well as an adult and pediatric infectious diseases fellowship. Resp. Ex. F at 2-3. He holds board certifications in pediatrics, internal medicine, infectious diseases, and pediatric infectious disease. Resp. Ex. C at 1; Resp. Ex. F at 2. Dr. Anderson works as a Professor at Emory University School of Medicine, and is an Attending Physician at Children's healthcare of Atlanta, Emory University Hospitals, and Grady Hospital. Resp. Ex. F at 1. He "continue[s] to provide clinical care for both adults and children with infectious diseases, teach, and conduct research. [His] research focuses on the epidemiology of infectious diseases and also on vaccine clinical trials." Resp. Ex. C at 1. Dr. Anderson "ha[s] been a principal investigator or co-investigator on over 40 clinical trials and ha[s] well over 100 publications." Id.; see also Resp. Ex. F at 17-43.

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[37] Dr. Wilfong suggested a "concurrent viral illness" as a second possible explanation in this case. Resp. Ex. A at 6. Dr. Wilfong raised this second explanation in the context of the medical record entries that referred to serum sickness as a differential diagnosis to explain Petitioner's symptoms. Id. Other than suggesting this possibility, Dr. Wilfong did not elaborate on this opinion.

[38] Micah T. McClain et al., The Role of Epstein-Barr Virus in Systemic Lupus Erythematosus, 6 Frontiers Bioscience e137 (2001).

[39] Dr. Anderson submitted two expert reports. Resp. Exs. C, H.

b. Opinion

i. Diagnosis

Dr. Anderson offered opinions about CFS[40] and its association with the EBV. He explained that "[a]lthough multiple definitions and names for [CFS] exist, none of them require prior EBV infection or reactivation." Resp. Ex. C at 4. He explained that CFS has been seen in patients after infections with giardia, *Campylobacter*, and Q-fever. Id. at 5. Dr. Anderson agreed that CFS has also been seen after infectious mononucleosis (which is caused by EBV). Id. While CFS may occur after EBV, Dr. Anderson opined that "no evidence exists for persistence or reactivation of EBV in patients with CFS[]." Id. Further, although the data suggests that "about 10% of patients after EBV will meet the definition of CFS[] at 6 months after infection (with additional declines occurring over time), ongoing CFS[] symptoms are not due to active EBV." Id. He explained that this means "EBV can serve as the trigger for CFS[], but does not drive ongoing CFS[] symptoms." Id.

ii. Loving Factor Four/Althen Prong One

The first mechanism proposed by Petitioner's expert, Dr. Bellanti, is that vaccination somehow induced epigenetic changes which may have played a role in EBV reactivation. Dr. Anderson agreed that "epigenetic changes . . . may regulate latency versus reactivation," but he did not agree that "these epigenetic changes in EBV-infected cells occur[] after Tdap vaccination." Resp. Ex. C at 6. He noted there is no medical literature support for such a theory. Id. Dr. Anderson confirmed that "[a] PubMed[41] search did not identify any articles linking EBV epigenetic changes with tetanus, diphtheria, or pertussis containing vaccines." Id. He also reviewed all of Petitioner's medical literature and did not find any support for any the idea that the Tdap vaccine, and the bacterial proteins in it, could cause EBV epigenetic changes. Id.

Further, while Dr. Anderson stated that "biological agents can trigger EBV viral reactivation at the cellular level *in vitro*," this has not been true *in vivo*. Resp. Ex. C at 6. He cited papers by Murata[42] and Murata and Tsurumi[43] to establish that the "[p]hysiological stimuli that trigger viral reactivation *in vivo* have not been clearly identified." Id. at 4, 6 (quoting Resp.

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[40] Dr. Anderson also referred to CFS as systemic exertion intolerance disease (SEID). Resp. Ex. C at 4. The illness will be called CFS throughout this Decision.

[41] "PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature . . . . The PubMed database contains more than 34 million citations and abstracts of biomedical literature." Nat'l Libr. Med., Nat'l Ctr. for Biotechnology Info., PubMed Overview, https://pubmed.ncbi.nlm.nih.gov/about/ (last visited Oct. 12, 2022).

[42] Takayuki Murata, Regulation of Epstein-Barr Virus Reactivation from Latency, 58 Microbiology & Immunology 307 (2014).

[43] Takayuki Murata & Tatsuya Tsurumi, Switching of EBV Cycles Between Latent and Lytic States, 24 Revs. Med. Virology 142 (2014).

Ex. C-14 at 2) (citing Resp. Ex. C-13 at 2). The papers identified several biological reagents (TPA, calcium ionophore, sodium butyrate, anti-Ig, and TGF-ß) that can stimulate EBV reactivation *in vitro*. Id. at 4 (citing Resp. Ex. C-13 at 2; Resp. Ex. C-14 at 2). But, as described by Dr. Anderson, this is not relevant in the context of vaccination. Id. at 4, 6.

Dr. Anderson next addressed Dr. Bellanti's second theory, that vaccination led to dysregulation of antigen presenting cells (microglia, dendritic cells, B-Cells), which led to CD8+ T cell activation, causing EBV reactivation. In support of this theory, Dr. Bellanti cited papers by Eligio et al. and Aligo et al. Dr. Anderson agreed that CD8+ T cells play an important role in controlling the initial primary EBV infection. Resp. Ex. C at 6. He disagreed, however, that there was evidence here of immune system dysfunction as described in Eligio et al. Id.; Resp. Ex. H at 1. He also disagreed that Aligo et al. was relevant, as it did not mention vaccination, tetanus, diphtheria, or pertussis. Resp. Ex. C at 6.

The third causal mechanism proffered by Dr. Bellanti was molecular mimicry. Dr. Anderson explained that "[a]lthough the EBV genome encodes nearly 100 viral proteins, these do not necessarily share epitopes with human proteins." Resp. Ex. H at 1-2 (internal citations omitted). He emphasized that none of the articles cited by Dr. Bellanti "discuss cross reactivity between various antigens in the Tdap vaccine, EBV, and human cells." Id. at 2. Dr. Anderson added that "[w]hile Kempkes [and Robertson] does mention environmental stimuli as a cause of occasional EBV reactivation from latency, he does not state that vaccination can trigger this reactivation." Id. (internal citations omitted) (citing Pet. Ex. 54). Further, Dr. Anderson opined that "[t]here is no evidence to connect molecular mimicry with Tdap vaccination and [MCTD] or EBV reactivation." Resp. Ex. C at 7.

In summary, Dr. Anderson opined that

- EBV can serve as a trigger for CFS[], but does not contribute to ongoing CFS[] symptoms through active replication or reactivation, and it is not clear [P]etitioner has CFS[].
- No data suggest that Tdap vaccination is associated with EBV reactivation despite millions of doses having been administered.
- No data suggest that Tdap vaccination can cause or worsen CFS[].
- No data suggest that Tdap can cause or worsen MCTD.
- Thus, there is no data supporting the purported link between Tdap vaccination and EBV reactivation with subsequent EBV-related worsening of either CFS[] or MCTD.

Resp. Ex. C at 7.

iii. Loving Factor Five/Althen Prong Two

Critical to her theories of causation, Petitioner posited that her vaccination caused a reactivation of her EBV, to which Dr. Anderson disagreed. Resp. Ex. H at 1. Dr. Anderson opined that "there is no data in [Petitioner's] available medical records supporting the statement that more likely than not [] she had reactivation of her latent EBV." Id. "Although EBV is noted

in her past medical history, no treating physician associated EBV with her current clinical condition. No testing by her treating physicians was even sent to evaluate for EBV reactivation." Id. Dr. Anderson concluded that "[t]o suggest that [Petitioner's] illness was due to EBV reactivation is completely speculative." Id.

In support of this conclusion, Dr. Anderson explained that Petitioner's "medical records do not include any lab results showing that the [P]etitioner suffered a post-vaccination reactivation of EBV." Resp. Ex. C at 1. He discussed the methods by which EBV reactivation is diagnosed. Id. at 3-4. EBV infection is generally diagnosed through antibody testing. Id. at 3. "Antibodies are directed against several antigens including the surface protein of the viral capsid antigen (VCA), early antigen (EA), and nuclear antigen (NA)." Id. An acute EBV infection is "diagnosed by the presence of EBV VCA IgM (with or without EBV VCA IgG) and the absence of EBNA IgG . . . . EBV VCA IgM will disappear after acute infection, but EBV VCA IgG and EBNA IgG will remain present for life." Id.

Based on his review of Petitioner's records, Dr. Anderson opined that Petitioner "may have had acute EBV infection in 1981 [and] 1985 []as . . . she appears to have had a clinical syndrome potentially consistent with mononucleosis based upon available documentation." Resp. Ex. C at 5. The only antibody results documented in her medical records show that on June 15, 1992, she had an EBV IgG 295 and an EBV IgM < 100. Id. at 6. According to Dr. Anderson, these results showed Petitioner had an EBV infection at some point before June 1992. Id. However, he found no antibody test result that evidenced EBV reactivation at any time after Petitioner's Tdap vaccination on August 11, 2014. Id. at 5. Although there is a reference to a titer of 2850 in the record on July 18, 2013, prior to vaccination, Dr. Anderson explained that there is no information about the date of this result, and it is not known whether this result is for EBV VCA IgM, EBV VCA IgG, or EBNA IgG. Id. Therefore, this number is not evidence of EBV reactivation. Id.

Further, he noted reactivation occurs in patients who are critically ill, with conditions like septic shock, or in patients who are severely immunocompromised (such as patients who receive drug therapy for organ transplantation). Resp. Ex. C at 4. Dr. Anderson explained, however, that vaccines "are not known to be associated with EBV reactivation." Id. Moreover, Dr. Anderson noted "[P]etitioner's immune system was able to control her initial infection with EBV," and "[t]here is no evidence [that she had] a CD8+ deficiency or dysregulation." Id. at 6.

EBV reactivation can be detected through diagnostic testing, including PCR testing for EBV, or "detection of IgG directed against early antigen (EA-IgG) or VCA IgM." Resp. Ex. C at 4. However, Dr. Anderson stated that none of these tests were ordered for Petitioner after she received the Tdap vaccination. Id. In summary, he concluded "there are no data supporting EBV reactivation as having occurred in the [P]etitioner after Tdap vaccination." Id. at 6.

In addition to his opinion that there is no foundational support for EBV reactivation here, Dr. Anderson opined that Petitioner's clinical course does not demonstrate that her CFS worsened after vaccination. Resp. Ex. H at 2. He opined that

> [a] common feature of CFS[] is diminished exercise capacity. It is noted in [Petitioner's] medical record that:
>
> - She has documentation of exercise 4 – 5 days/week between 2012 – 2014 (Ex 1, page 100).
> - On 2/15/2012, she was documented [to] "exercise – walk/jo[g] 3 miles daily . . ." and "able to complete here (sic) workout for 3 miles. Was in military, used to be very active, now states she's 'building' it back up." (Ex 1, page 25)
> - On 6/13/2013 she stated that she "Ran 5 K in Dallas this year. Has been feeling energetic enough for these activities but will feel fatigued regularly as well." (Ex 1, page 21).

Id. at 2-3.

Dr. Anderson opined that if the Tdap vaccination she received in August 2014 had worsened her CFS, "it would be expected that this impact would be sustained and not waxing/waning." Resp. Ex. H at 3. Instead, Petitioner "had improvement in her exercise capacity by 4/20/16 with ability to walk 5 miles daily." Id. (emphasis omitted) (citing Pet. Ex. 1 at 5). Dr. Anderson concluded that Petitioner's medical record does not support a finding that her CFS "severely impacted her functional status." Id.

Lastly, Dr. Anderson opined that Petitioner "has radiographic evidence of her clinical diagnosis of osteoarthritis, which is not related to vaccination." Resp. Ex. H at 4. He believed osteoarthritis was more likely than not the cause of her arthralgia. Id. In support of this opinion, Dr. Anderson provided a summary of relevant medical records. Id. at 3. On November 19, 2014, Petitioner was seen by Dr. Reyes. Id. (citing Pet. Ex. 3 at 6-7). Petitioner noted that she had morning stiffness lasting "about half an hour" and mild tenderness over some of the joints in her hands and feet. Pet. Ex. 3 at 6. Dr. Reyes documented that Petitioner had a diagnosis of osteoarthritis of her hands and feet. Resp. Ex. H at 3 (citing Pet. Ex. 3 at 6). On July 27, 2015, Petitioner had X-rays of her hands and feet. Id. (citing Pet. Ex. 19 at 7-8). The X-rays showed no fracture, dislocation, or subluxation, and "no significant degenerative changes." Id. (quoting Pet. Ex. 19 at 7-8).

Dr. Anderson opined that

> at no point around the time of Tdap vaccination does the [Petitioner] have arthritis present on examination (warm, swollen, tender joint or joints with fluid in the joint). Based on documentation, she has arthralgia (joint pain). Images of the joint do not demonstrate a destructive process, but both examination and also some images suggest a degenerative process. These findings fit with the clinical diagnosis of osteoarthritis that was diagnosed by Dr. Reyes . . . .

Resp. Ex. H at 3. Further, Dr. Anderson opined that "[o]steoarthritis is not due to immunizations or to EBV, but is rather due to cumulative wear and tear on the joint, a common issue among

those > 60 years of age." Id. He concluded that osteoarthritis is the most likely cause of Petitioner's complaints of arthralgia. Id. at 4.

iv. Loving Factor Six/Althen Prong Three

Dr. Anderson opined that there is no evidence that the Tdap vaccine can cause EBV reactivation, or that EBV reactivation can cause worsening of autoimmune diseases, CFS, or CTD. And he did not find evidence that Petitioner's Tdap vaccination caused EBV reactivation, or otherwise caused aggravation of any underlying illness which she may have had. He did not specifically offer any opinions as to whether there was any temporal association between Petitioner's Tdap vaccination and any worsening of her illnesses.

VI. LEGAL FRAMEWORK

A. Standard of Adjudication—Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

Despite the weight afforded to medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) ("[Section 13(b)(2)] must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them." (emphasis omitted)).

B. Standards for Adjudication—Causation

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley, 991 F.2d at 1575.

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum.

Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

To receive compensation through the Program, Petitioner must prove either (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that she suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Because Petitioner does not allege she suffered a Table Injury, she must prove a vaccine she received caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(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." Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all materials in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in her favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

C. Standards for Adjudication—Significant Aggravation

The elements of an off-Table significant aggravation case are set forth in Loving. See Loving, 86 Fed. Cl. at 142-44; see also W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the Loving case provides the correct framework for evaluating off-table significant aggravation claims"). The Loving court combined the Althen test, which defines off-Table causation cases, with a test from Whitecotton. Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995) (concerning on-Table significant aggravation cases). The resultant test has six components, which are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4).

VII. ANALYSIS

A. Diagnosis

As Federal Circuit precedent establishes, in certain cases it is appropriate to determine the nature of an injury before engaging in the Althen analysis. Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010). Since "each prong of the Althen test is decided relative to the injury[,]" determining facts relating to the claimed injury can be significant in a case where diagnosis is not clear. Id. Here, Petitioner asserts that she has an autoimmune condition with longstanding positive ANA and positive EBV that has been alternatively described a CTD, UCTD, MCTD, CFS, or an immunodeficiency illness. Respondent argues that Petitioner has not clearly established the nature of the illness which she alleges is vaccine-related, and that alleging an underlying autoimmune disorder is insufficient.

Dr. Bellanti opines that while Petitioner's condition is difficult to define, the diagnosis of UCTD comes the closest to describing her pre-vaccination condition. He also asserts that her illness is characterized by a longstanding positive ANA and positive EBV. As an alternative diagnosis, Dr. Bellanti believes that Petitioner's diagnosis falls into the category of "autoimmune conditions," which he asserts is the umbrella diagnosis for all CTDs.

Respondent's expert, Dr. Wilfong, did not disagree that Petitioner was diagnosed with UCTD. She also agreed that Petitioner had been diagnosed with CFS, although she was not sure that Petitioner met the diagnostic criteria for the illness. Regardless of Petitioner's diagnosis, Dr. Wilfong opined that vaccination did not worsen or aggravate her underlying conditions. Dr. Anderson did not offer opinions as to Petitioner's underlying diagnosis.

Petitioner's medical records establish that prior to vaccination on August 8, 2014, she had an acute EBV infection, likely in 1981 and 1985. Her records also establish that she did not have any diagnostic testing which established an acute EBV infection or reactivation after 1992. In addition to her history of EBV infection, Petitioner's records also show that she had a longstanding diagnosis of CFS.

Regarding myalgias and joint pain, Petitioner's records show that she complained of these symptoms in March 2012, prior to the vaccination at issue. Petitioner also had a positive ANA titer in July 2013, and on the day of vaccination in August 2014, diagnostic lab studies revealed that she had a positive RNP, a marker for a CTD. On August 20, 2014, she reported a six-month history of fatigue, and some aching in her joints, including her hands, knees and hips. Based upon the workup done by her rheumatologists, her positive ANA and anti-RNP, and her associated joint pain, she was diagnosed with UCTD.

Thus, the undersigned finds that Petitioner had two relevant diagnoses, CFS and UCTD prior to her vaccination. While the UCTD diagnosis was not documented in Petitioner's medical record until sometime after vaccination (October 2014, once she had a rheumatology workup), she had symptoms and positive serologies characteristic of the condition prior to vaccination.

B. Significant Aggravation

1. Loving Factor 1: What Was Petitioner's Condition Prior to Administration of the Vaccine?

The first step in the Loving test is to determine Petitioner's condition with regard to CFS and UCTD before she received her Tdap vaccination on August 8, 2014. First, as to Petitioner's EBV status, her medical records establish that long before her vaccination, she had an acute EBV infection, likely in 1981 and 1985. She did not have any diagnostic testing or other evidence of an acute EBV infection or reactivation after 1992.

In addition, Petitioner had longstanding CFS, dating back at least 30 years. Regarding myalgias and joint pain, Petitioner's records show that she complained of these symptoms in March 2012. Petitioner also had a positive ANA in July 2013, and on the day of vaccination (August 8, 2014), diagnostic lab studies revealed that she had a positive RNP, a marker for a CTD. On August 20, 2014, she reported a six-month history of fatigue, and some aching in her joints, including her hands, knees and hips. Based upon the workup done by her rheumatologists, her positive ANA and anti-RNP, and her joint pain, she was diagnosed with UCTD.

Thus, prior to vaccination on August 8, 2014, the undersigned finds that Petitioner had two relevant diagnoses, CFS and UCTD, prior to her vaccination. She had fatigue, and she sometimes had aching in her joints, including her hands, knees, and hips.

2. Loving Factor 2: What Is Petitioner's Current Condition (or Her Condition Following the Vaccination, If Also Pertinent)?

The second part of the Loving test is to discuss "the person's current condition (or condition following the vaccination if that is also pertinent)." Loving, 86 Fed. Cl. at 144. Here, Petitioner's condition following vaccination is most pertinent.

Less than two weeks after Petitioner's Tdap vaccination in August 2014, Petitioner complained of "always being tired for 6+ months," sometimes experiencing achy joints in hands, knees, and hips, as well as "fever, chills, aches, and fatigue." Pet. Ex. 16 at 64. Physical examination was normal. One month after Petitioner received the TdaP vaccination, on September 9, 2014, she reported night sweats, headaches, whole-body joint pain, and fatigue. Physical examination revealed tenderness in her hands. Approximately one week later, on September 16, 2014, physical examination revealed good range of motion in all of Petitioner's major joints, no joint swelling or redness, normal strength, and mild bony hypertrophy. Dr. Said questioned whether Petitioner had experienced serum sickness post-vaccination. If so, her condition was improved. By the end of September 2014, minimal edema was observed in the small joints of her hands.

Based on rheumatology workup done in October 2014, Petitioner had positive serologies for UCTD and associated joint pains. Other serologic markers for any specific CTD were negative. Petitioner's joint pain was more pronounced after vaccination. X-rays showed early osteoarthritis and in November 2014, Petitioner was diagnosed with osteoarthritis, and there was no indication that it was related to her vaccination. Physical examination in November 2015 showed mild tenderness over some joints in Petitioner's hands and feet, but no swelling or redness. She had a mild decrease in strength in her hips and shoulders.

Moving forward to February 2016, Petitioner had minimal chronic synovitis in the joints in her hands. On November 16, 2016, she had completed two years of monitoring by Dr. Reyes, and she had not developed any specific CTD. Dr. Reyes discontinued monitoring her for MCTD.

Petitioner had some acute symptoms after she received her Tdap vaccination that raised the question of whether she had a serum sickness-like reaction. Those symptoms resolved by September 16, 2014, and she had good range of motion in all major joints, with no objective joint swelling or redness. She also had normal strength. By October 23, 2014, she was feeling better overall, except for some pain in her finger joints. Physical examination did not show active swelling or synovitis. She had no serological markers to suggest any worsening of her underlying CTD. She was diagnosed with early osteoarthritis, but Petitioner has not alleged that her osteoarthritis is vaccine-related, and she is not seeking compensation for that condition. Her expert, Dr. Bellanti, has not asserted that her osteoarthritis is related to her Tdap vaccine. And no treating physician attributed it to her vaccination.

Thus, the undersigned finds that after vaccination, Petitioner had an acute illness that was characterized as serum sickness-like, which was short lived, and resolved. She also had some worsening of joint pain in the hands and feet. She did not have any worsening of her fatigue. Also, her underlying UCTD did not evolve into a distinct CTD or MTCD. In conclusion, Petitioner had an increase or aggravation of her joint pain, which was a symptom of her underlying CTD.

However, the records do not show that Petitioner had any worsening of her fatigue post-vaccination. To the extent that she had a flare of her CFS, it began approximately six months

prior to her vaccination. On August 20, 2014, less than two weeks after vaccination, Petitioner saw Dr. Seymour and complained of "always being tired for 6+ months." Pet. Ex. 16 at 64.

Additionally, Dr. Anderson explained that a common characteristic of CFS is reduced exercise capacity. He cited medical records where Petitioner reported that she exercised four to five days per week from 2012 through 2014. See Pet. Ex. 1 at 100. In June 2013, she ran a 5K, and reported "feeling energetic enough for these activities but will fatigue regularly as well." Id. at 21. After vaccination, she was able to walk five miles daily by April 2016. On this point, the undersigned finds Dr. Anderson's opinions persuasive. Since Petitioner did not have worsening of her fatigue and was able to return to walking long distances on a regular basis post-vaccination, the undersigned finds that there is insufficient evidence to show that she had an aggravation of her CFS post-vaccination.

In conclusion, the undersigned finds that the Petitioner had an increase in joint pain, which was a symptom of her underlying CTD after her Tdap vaccination.

In reaching the above findings, the undersigned considered Petitioner' testimony set forth in her affidavit as well as the histories she provided to physicians. For example, Petitioner averred that she complained of joint pain following vaccination. See Pet. Ex. 12 at ¶¶ 5-6. Additionally, Petitioner continuously complained of joint pain, mostly in her hands, knees, and hips. See Pet. Ex. 16 at 64 ("Sometimes her joints ache, in hands, knees, and hips."); Pet. Ex. 16 at 65 (reporting joint pain); Pet. Ex. 7 at 1 ("She . . . states [that] the day after [vaccination] she developed severe swelling of her joints, red, hot, and swollen . . . . [She] feels that her hands in particular are still painful and has felt that they hurt more than they did prior to the Tdap vaccine."); Pet. Ex. 16 at 66 (noting a finding of minimal edema in the small joints of Petitioner's hands on physical examination).

To the extent that Petitioner's affidavit or histories noted in the medical records are inconsistent with and contradicted by the physicians' objective physical examinations or diagnostic testing, the undersigned defers to the physician findings as the most reliable source of information. See Cucuras, 993 F.2d at 1528 (noting that "the Supreme Court counsels that oral testimony in conflict with contemporaneous documentary evidence deserves little weight"); Doe/70 v. Sec'y of Health & Hum. Servs., 95 Fed. Cl. 598, 608 (2010); Stevens v. Sec'y of Health & Hum. Servs., No. 90-221V, 1990 WL 608693, at *3 (Cl. Ct. Spec. Mstr. Dec. 21, 1990) (noting that "clear, cogent, and consistent testimony can overcome such missing or contradictory medical records"); Vergara v. Sec'y of Health & Hum. Servs., No. 08-882V, 2014 WL 2795491, at *4 (Fed. Cl. Spec. Mstr. May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded in later medical histories, affidavits, or trial testimony.").

The undersigned does not rely on the VA Disability Rating Decisions, either pre- or post-vaccination, or find them to be persuasive evidence of Petitioner's condition before or after vaccination for several reasons. The disability ratings did not occur contemporaneously before

or after the vaccination[44] at issue, and therefore, are less informative and reliable than the contemporaneous medical records. Additionally, it is not clear that all of the records, application forms, correspondence, and contract examinations used by the VA to determine Petitioner's disability rating have been filed in the instant action, and to the extent they have not been filed, the undersigned has not reviewed them.[45] Moreover, the criteria used by the VA to make its disability determinations are not included in the VA Decision or in Petitioner's VA records, or otherwise available.

Further, the VA Disability Rating Decisions are not binding on this Court, either by statute, regulation, or precedential case law. Petitioner acknowledges this point in her motion and supporting memorandum. See Pet. Mot. at 18.

Perhaps the most compelling reason that the undersigned has not based her findings on the VA Disability Rating Decisions is that it includes information that is inconsistent with the contemporaneous medical records. In its decision, the VA states that Petitioner has a MCTD. Pet. Ex. 4 at 2. However, Petitioner's records, and specifically the records of Dr. Reyes, establish that Petitioner was monitored by Dr. Reyes for a two-year period following vaccination to ensure that her CTD did not worsen or evolve into MCTD, and it did not. Next, the VA Disability Rating Decision states that Petitioner had "residuals of [EBV]," but no diagnostic tests were done to verify that to be true. Id. The characterization of Petitioner's fatigue and muscle and joint pain is inconsistent with what is described in her medical records. And lastly, a rating criteria for lupus was used, and described as an "acute disease, with frequent exacerbations, producing severe impairment of health." Id. at 50. Petitioner, however, has not been diagnosed with lupus.

3. Loving Factor 3: Does Petitioner's Current Condition (or Condition After Vaccination) Constitute a "Significant Aggravation" of Her Condition Prior to Vaccination?

The next factor of the Loving test is to determine whether there is a "significant aggravation" of Petitioner's condition by comparing her condition before vaccination to her condition after vaccination. The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4). Using this definition, the undersigned finds that, based on all of the facts and circumstances here, Petitioner had a significant aggravation of her underlying CTD.

Petitioner's records establish that after her Tdap vaccination, she had a significant increase in her joint pain, especially in her hands, that she took Medrol daily, as well as pain medication (low-dose Naltrexone). In 2016, Dr. Plata prescribed Plaquenil for her joint pain, with tramadol for flare-ups. Petitioner did not begin taking the Plaquenil, however, until 2017.

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[44] The initial VA disability rating of 10% was issued, and the rating was increased to 100% post-vaccination on July 22, 2016, effective December 31, 2015. Pet. Ex. 4 at 1-2, 4.

[45] For a complete list of evidence used by the VA, see Pet. Ex. 4 at 3; Pet. Ex. 62 at 219.

Her joint achiness improved on the medication. In 2017, Dr. Plata characterized her UCTD as a "mild disease," with "constitutional symptoms that are mild, but . . . annoying." Pet. Ex. 19 at 58. Although her disease was described as mild, Petitioner's pain required the use of steroids, pain medication, and Plaquenil. The undersigned finds that the aggravation of her illness resulted in pain which constituted a substantial deterioration of her health. Thus, she meets the criteria of Loving Factor Three.

4. Loving Factor Four/Althen Prong One: Medical Theory of Causation

The fourth Loving factor has its origins in Althen Prong One, and Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1379; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019); see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d 1339 at 1347 ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner has failed to establish a sound and reliable medical theory for how the Tdap vaccine can cause significant aggravation of her underlying autoimmune disorder by preponderant evidence for several reasons.

Dr. Bellanti offers a two-step mechanistic theory. The first step is that the Tdap vaccine can cause EBV reactivation. The second step is that EBV reactivation can cause a significant aggravation of autoimmune disorders, including CFS and/or UCTD.

Regarding the first step, that the Tdap vaccination can cause EBV reactivation, Dr. Bellanti posits three theories. First, he opines that the Tdap vaccine can trigger reactivation via epigenetic changes. He states that the "presumption is that [reactivation] occurs when latently infected B cells respond to unrelated infections." Pet. Ex. 63 at 17. Through this statement, he seems to infer that vaccination is the same as an "unrelated infection." But he did not cite any medical literature or other evidence to flesh out this theory or show that vaccination can act as an unrelated infection. The article by Odumade et al., cited by Dr. Bellanti in support of this theory, did not suggest that vaccines can act as "unrelated infections," or that vaccines play any role in causing reactivation. Further, Dr. Bellanti does not explain how a vaccine in general, or the Tdap vaccine specifically, changes or alters the expression of EBV so as to cause reactivation. The undersigned therefore finds this theory to be unsupported by medical or scientific facts, research, or any other reliable evidence.

Dr. Bellanti's second theory is based on the idea that the vaccination can cause "dysregulation of microglia, dendritic cells, B-cells" due to specific antigens, excipients, aluminum, or endotoxins in the vaccine, "leading to CD8+ T cell activation." Pet. Ex. 48 at 5; Pet. Ex. 63 at 16. The paper he cites by Eligio et al. did not discuss vaccines, or explain how aluminum and/or endotoxins play a role in EBV reactivation. Dr. Bellanti did not offer any evidence to establish that the Tdap vaccine, or any ingredient in the vaccine, can lead to CD8+ T cell activation so as to cause EBV reactivation. He did not provide basic foundational evidence to show that aluminum is in the vaccine, or that it if it is, it can cause reactivation. The same is true for his allegation regarding endotoxins in the vaccine. He did not identify any endotoxins in the vaccine. This theory was not developed enough for the undersigned to reach any reasonable conclusions about its relevance or reliability.

Dr. Bellanti's third theory is based on molecular mimicry. He did not identify any medical literature, or other evidence, to support his opinion that molecular mimicry is a viable theory for EBV reactivation.[46] Nor did he explain how molecular mimicry could trigger EBV reactivation. He cited Kanduc and Shoenfeld to suggest that homologous peptide sequences between the vaccine and the EBV "might confound, intensify[,] or weaken the human immune responses" post-vaccination, or otherwise "imprint the host immunological memory." Pet. Ex. 53 at 2, 7. Kanduc and Shoenfeld, however, did not address the Tdap vaccination or how it could confound, intensify, or weaken the immune system so as to cause reactivation. Dr. Bellanti does not identify any possible avenues of homology between the vaccine and the latent virus. Further, he does not explain how molecular mimicry would lead to viral reactivation.

The Kanduc and Shoenfeld paper aimed to analyze "peptide commonality among viral . . . pathogens, and the immunopathologic consequences in the human host." Pet. Ex. 53 at 1. The authors analyzed several viruses and bacteria for "common amino acid sequences that are [] shared with the human host." Id. However, EBV was not studied. The authors did not address any homology or similar peptide sequences between the Tdap vaccine and humans. EBV reactivation was not addressed. The article does not appear to be relevant to whether molecular mimicry may be a possible mechanism for EBV reactivation.

In the concluding discussion of the article, the authors question whether "minimal epitope determinants among pathogens," including EBV, "and the consequent potential cross-reactivity might represent the molecular basis and mechanism by which different infections over time can irrevocably imprint the host immunological memory, thus leading to subsequent anamnestic, misled, immune responses." Id. at 6-7. The authors suggest this is a way to think about why vaccines sometime fail or cause adverse events. This notion that host immunity can be affected over time by prior infections or vaccinations, without more foundational evidence, does not explain how the Tdap vaccine could cause EBV reactivation. There is no evidence that the Petitioner had any particular immunological memory which rendered her susceptible to an adverse reaction to the Tdap vaccination. The undersigned finds this theory to be lacking in

[46] Of note, Eligio et al. explains that "[o]f the nearly 100 viral genes that are expressed during [EBV] replication, only 10 are expressed in latently infected B cells *in vitro*." Pet. Ex. 52 at 5. This information suggests that Dr. Bellanti is incorrect, and it does not support the idea that molecular mimicry is an attractive theory for how a vaccine could trigger EBV reactivation.

relevance to the facts and circumstances here. As such, this is a conclusory opinion without foundational evidence to support it. [47]

When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck v. Sec'y of Health & Hum. Servs., No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, decision aff'd, 141 Fed. Cl. 138 (2018), aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert." Prokopeas v. Sec'y of Health & Hum. Servs., No. 04-1717V, 2019 WL 2509626, at *19 (Fed. Cl. Spec. Mstr. May 24, 2019) (quoting Moberly, 592 F.3d at 1315). Instead, special masters are expected to carefully scrutinize the reliability of each expert report submitted. See id.

In addition to offering conclusory opinions, Dr. Bellanti mischaracterizes the medical literature he cites, suggesting that articles support his opinion that vaccines are known to trigger EBV reactivation, when the authors did not address the issue. In fact, none of the articles cited by Dr. Bellanti discuss a mechanism whereby vaccines can cause EBV reactivation. For example, Aligo et al. make no reference to vaccines playing a role in viral reactivation. See Pet. Ex. 50. The paper by Eligio et al. is a very comprehensive discussion of EBV and the diseases it causes, but it makes no reference to vaccines. See Pet. Ex. 52.

Kempkes and Robertson focus on EBV-related malignancies but make no mention of how vaccines could cause reactivation. See Pet. Ex. 54. Noor et al. provide a comprehensive review of CFS, and discuss possible triggering events such as infections, which are followed by immune dysregulation. However, they do not suggest that vaccines play a role in EBV reactivation, or cause, or contribute to exacerbation of CFS. See Pet. Ex. 66. Ultimately, Dr. Bellanti concedes that there is no literature "that directly relates EBV reactivation to Tdap vaccinations, or Tdap to [MCTD]." Pet. Ex. 63 at 21. But Dr. Bellanti's tendency to stretch the application of medical literature too far renders his opinions less persuasive.

Further, opining that molecular mimicry is a causal theory, without more, is insufficient. See, e.g., McKown v. Sec'y of Health & Hum. Servs., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (explaining that "merely chanting the magic words 'molecular mimicry' in a Vaccine Act case does not render a causation theory scientifically reliable, absent additional evidence specifically tying the mechanism to the injury and/or vaccine

[47] This is not the first time Dr. Bellanti has been criticized for conclusory opinions. See, e.g., Temes v. Sec'y of Health & Hum. Servs., No. 16-1465V, 2020 WL 4198036, at *20-21 (Fed. Cl. Spec. Mstr. May 12, 2020) (finding Dr. Bellanti made "conclusory statements . . . [with] no reliable literature [] offered" for support, he "did not substantiate his contention[s]," and "his theories were too thin"), mot. for rev. denied, 151 Fed. Cl. 448; Miles v. Sec'y of Health & Hum. Servs., No. 12-254V, 2018 WL 3990987, at *46-49 (Fed. Cl. Spec. Mstr. June 28, 2018) (criticizing Dr. Bellanti's theory and finding it was based on speculation), mot. for rev. denied, 142 Fed. Cl. 136, aff'd, 769 F. App'x 926 (Fed. Cir. 2019); Brook v. Sec'y of Health & Hum. Servs., No. 04-405V, 2015 WL 3799646, at *15-16 (Fed. Cl. Spec. Mstr. May 14, 2015) (finding Dr. Bellanti's opinions conclusory and speculative).

in question" (emphasis omitted)); Johnson v. Sec'y of Health & Hum. Servs., No. 14-254V, 2018 WL 2051760, at *26 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) ("Petitioners cannot simply invoke the concept of molecular mimicry and call it a day. Rather, they need to offer reliable and persuasive medical or scientific evidence of some kind (whether expert testimony or literature) . . . . (internal citations omitted) (emphasis omitted)); Mattus-Long v. Sec'y of Health & Hum. Servs., No. 15-113V, 2022 WL 4242140, at *27 (Fed. Cl. Spec. Mstr. Aug. 31, 2022) (noting "the mere mention of molecular mimicry is not a 'get out of jail free card' in the Program, entitling claimants to compensation, merely because it has scientific reliability as a general matter"); Sheets v. Sec'y of Health & Hum. Servs., No. 16-1173V, 2019 WL 2296212, at *17 (Fed. Cl. Spec. Mstr. Apr. 30, 2019) (determining Petitioner had not satisfied Althen prong one when he did not relate molecular mimicry "to either the vaccines in question or Petitioner's own specific condition").

The second step of Dr. Bellanti's mechanistic theory is that EBV reactivation can cause a significant aggravation of autoimmune disorders—here, CFS and/or UCTD. Since he failed to prove the first step of his theory, there is no foundational support for the second step. Moreover, Dr. Bellanti does not explain how EBV, once reactivated, causes significant aggravation of CFS or UCTD.

For the above reasons, the undersigned finds that Petitioner has not established by preponderant evidence that a Tdap vaccine can cause EBV reactivation so as to lead to significant aggravation of CFS or UCTD.

5. Loving Factor Five/Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, and Loving Factor Five, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Regarding the fifth Loving factor/second Althen prong, the undersigned finds that because Petitioner failed to prove by preponderant evidence that the Tdap vaccination can cause EBV reactivation, she is also unable to prove that the vaccination caused her to have a reactivation of EBV. Dr. Anderson provides the most cogent, sound, and reliable opinions on this aspect of causation, and the undersigned thus finds his opinions most persuasive.

First, Dr. Anderson opines that although Petitioner had a history of EBV, her medical records do not include any lab results, or other diagnostic tests, showing that she had a post-vaccination reactivation of her EBV. He explained that EBV reactivation is diagnosed through antibody tests. An acute infection is characterized by EBV VCA IgM and the absence of EBNA IgG. Based on Dr. Anderson's review of Petitioner's records, she may have had acute EBV in 1981 and 1985, when she was noted to have acute mononucleosis. The only antibody results in her records show that on June 15, 1992, Petitioner's EBV IgG was 295 and her EBV IgM<100. Thus, Dr. Anderson concluded that Petitioner had an acute infection some time before 1992, but there is no evidence that she ever had reinfection/reactivation at any time after her Tdap vaccination.

None of Petitioner's numerous physicians, including her two rheumatologists, documented that they ever suspected a diagnosis of acute EBV infection/reactivation. None of Petitioner's physicians ordered diagnostic testing for EBV reactivation. There are no antibody test results in the Petitioner's record to show that she had EBV reactivation after her vaccination. Therefore, the undersigned agrees with Dr. Anderson that it is speculative to conclude that Petitioner had EBV reactivation at any time post-vaccination.

Petitioner's theory of causation hinges on EBV reactivation. She has failed, however, to prove that she had EBV reactivation, and thus, she has failed to prove that her Tdap vaccination significantly aggravated her underlying autoimmune illness.

This finding is consistent with what is known about EBV reactivation. After a primary EBV infection, once the infection is controlled by the immune response, the virus remains latent, usually for the lifetime of the host, unless the host is immunocompromised. Examples of immunosuppressed hosts include organ transplant recipients, those who have HIV infections, and patients with drug-induced immunosuppression. Reactivation may also occur in patients with critical illness like septic shock.

Dr. Anderson persuasively explained that Petitioner's immune system was able to control her initial EBV infection and that there is no evidence in her records to establish that she had a CD8+ deficiency or dysregulation. Petitioner was not an organ donor recipient, she did not have drug-induced immunosuppression, and she was not septic or critically ill. She did not belong to any category of patients known to be susceptible to EBV reactivation.

As explained by Dr. Wilfong, in July 2013, Dr. Rea ordered labs due to the concern about immune dysregulation. Petitioner's immunoglobulin and lymphocytes were tested, and the results were normal. There is no diagnostic evidence in Petitioner's records to establish that she had an immune dysregulation.

In summary, the undersigned finds that Petitioner did not belong to any category of patients who would be at risk for EBV reactivation, that she did not have an immune dysregulation that would predispose her to EBV reactivation, and she did not have evidence of EBV reactivation based on any concern, suspicion, or diagnostic testing.

Dr. Bellanti asserts that Petitioner had a serum sickness-like reaction that overwhelmed her immune system, and this caused her EBV reactivation. But as described above, there is no evidence that Petitioner's immune system was overwhelmed, or that she had EBV reaction/reactivation. Therefore, the undersigned rejects Dr. Bellanti's assertion.

Moreover, as explained by Dr. Wilfong, serum sickness is a type III hypersensitivity reaction with complement system activation. Petitioner did not have abnormally low C3 or C4 levels which would be indicative of the illness. Therefore, there is no evidence that she had a serum sickness reaction post-vaccination.

In September 2014, Dr. Said noted that Petitioner's joint pain "may represent serum sickness after she had the T[d]ap vaccine." Pet. Ex. 7 at 3. Petitioner's history of allergies noted in a record from December 2016 included "[Tdap] vaccine - serum sickness reaction." Pet. Ex. 16 at 78. The undersigned finds these statements in Petitioner's records, without more, do not meet the level of preponderant evidence. See § 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.67 (2009) ("[T]here 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."). Additionally, Petitioner's treating physicians, including her rheumatologists, consistently treated Petitioner for CFS or a CTD, not serum sickness.

Lastly, Respondent asserts there is an alternate cause of Petitioner's joint pain, unrelated to her vaccination. Specifically, Dr. Anderson opined that osteoarthritis is more likely than not the cause of Petitioner's arthralgia. In November 2014, Petitioner reported having 30 minutes of morning stiffness and subsequent X-rays showed degenerative changes consistent with osteoarthritis. Also, Dr. Reyes diagnosed Petitioner with osteoarthritis. Dr. Anderson agrees that Petitioner's joint stiffness and X-rays suggest a degenerative process consistent with osteoarthritis. Further, osteoarthritis is not caused by vaccination, but is common in those over 60 years of age due to wear and tear of joints.

While the undersigned agrees that Dr. Reyes did make a diagnosis of osteoarthritis, this diagnosis did not supersede or replace Petitioner's diagnosis of CTD. Regardless, the Petitioner has failed to prove a mechanistic theory, and she has failed to prove that she had EBV reactivation after her vaccination. For these reasons, the undersigned finds that Petitioner has failed to provide preponderant evidence of Loving Factor Five/Althen Prong Two, that her underlying autoimmune disease was significantly aggravated by her Tdap vaccination.

6. Loving Factor Six/Althen Prong Three: Proximate Temporal Relationship

The last element in the six-part Loving test has origins in Althen Prong Three. As stated in Loving, this element is "a showing of a proximate temporal relationship between vaccination and the significant aggravation." 86 Fed. Cl. at 144. Althen Prong Three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. A proximate temporal relationship has been equated to mean a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

Based on the case law cited above, this Prong/Factor consists of two parts. The Petitioner must first establish the time frame within which it is medically acceptable to infer causation. And secondly, she must show that the onset of the worsening or aggravation of her illness occurred during this time frame.

Petitioner received her Tdap vaccination on August 8, 2014. She states that the following day, she had severe swelling in her joints, with redness and warmth. She also reported fever and feeling ill. Dr. Bellanti opined that this onset was appropriate for "the initial immune-mediated response and the subsequent exacerbation of her condition." Pet. Ex. 63 at 24-25. Thus, the Petitioner asserts an onset of one day.

Dr. Bellanti proffered three mechanisms for how the Tdap vaccination can cause EBV reactivation. The first is based on epigenetics, or changes in the expression of genes triggered by "unrelated infections." Other than his general opinion that onset was appropriate here, Dr. Bellanti did not provide an opinion about the medically acceptable time within which this mechanism could occur. However, this theory is premised on the notion that "B-cell receptor stimulation triggers reactivation in B-cell lines." Pet. Ex. 63 at 17 (quoting Pet. Ex. 55 at 3).

The paper by Odumade et al. describes the primary response to an acute infection in EBV. The viral infection is spread through exposure to oral secretions or blood, and it takes approximately five to seven weeks for the primary EBV infection to cause symptoms of infectious mononucleosis. Pet. Ex. 55 at 6. During this long incubation period there is viral replication. Id. Odumade et al. state that after primary infection, the virus is latent in B lymphocytes as well as epithelial cells. And "viral gene expression patterns differ when the virus emerges from epithelial cells versus B cells." Id. at 6. Eligio et al. describe reactivation of the

latent EBV infection, explaining that it "involves the production of new virions[48] and eventually the 'shedding' of complete viral particles." Pet. Ex. 52 at 3.

Given the lengthy period between exposure and onset of infectious mononucleosis in acute EBV infection, and the description of reactivation of latent EBV reactivation which includes the production of virus (viral replication), it is difficult to imagine a scenario where latent EBV could become active and replicate sufficiently to cause acute symptoms in the span of one day.

The second mechanism proposed by Dr. Bellanti is that Petitioner had an immune deficiency, such as a CD8+ T cell deficiency, and that her vaccination triggered EBV reactivation due to her underlying immune deficiency. Dr. Bellanti did not offer an opinion about a specific appropriate temporal interval that would be expected given this mechanism. But, again, a period of viral replication would be necessary prior to symptom onset, as described above. And a one-day onset does not appear to be appropriate.

As for Dr. Bellanti's theory based on molecular mimicry, he did not offer any supportive literature or other evidence to support an onset of one day, nor has this onset been found to be supported in other cases. See, e.g., Castenada ex rel. N.A.C. v. Sec'y of Health & Hum. Servs., No. 15-1066V, 2020 WL 3833076, at *27-30 (Fed. Cl. Spec. Mstr. May 18, 2020) (finding onset of PANS 24 hours after vaccinations "is not consistent with the adaptive immune response inherent in the theory of molecular mimicry"), mot. for review denied, 152 Fed. Cl. 576; Hock v. Sec'y of Health & Hum. Servs., No. 17-168V, 2020 WL 6392770, at *28-29 (Fed. Cl. Spec. Mstr. Sept. 30, 2020) (finding a 24-hour onset of rheumatoid arthritis post-vaccination to be "entirely too fast for a disease process dependent on molecular mimicry to occur"). The undersigned agrees with the reasoning in these cases, and finds them consistent with her knowledge and experience gained from adjudicating other cases.

In summary, Petitioner alleges an onset of one day after vaccination. Although Dr. Bellanti opined this was appropriate, he did not file any evidence to support his opinion. The medical literature filed by both parties suggests that the incubation prior for an initial EBV infection is long. Viral replication is required in both the acute infection, and when EBV is reactivated from its latent phase. The process of viral replication is not described as occurring within one day. Moreover, Petitioner did not provide evidence to support a one-day onset given the mechanism of molecular mimicry. Therefore, the undersigned finds that Petitioner has failed to establish by preponderant evidence that a one day is appropriate given the mechanisms proffered.

[48] A virion is "the complete viral particle, found extracellularly and capable of surviving in crystalline form and infecting a living cell; it comprises the nucleoid (genetic material) and the capsid." Virion, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=53208 (last visited Oct. 5, 2022).

VIII. CONCLUSION

It is clear that Petitioner has had a very difficult struggle with her health, and the undersigned extends her sympathy to her. The undersigned's Decision, however, cannot be decided based upon sympathy, but rather on the evidence and law.

For all of the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that the Tdap vaccination significantly aggravated her underlying autoimmune condition. Therefore, Petitioner is not entitled to compensation and her petition must be dismissed.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master