In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 16-1422V
Filed: October 12, 2022
PUBLISHED

SHARON VOLPE, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner Cause-in-Fact; Significant Aggravation; Denial of Entitlement; Influenza Vaccine; Undifferentiated Connective Tissue Disease (UCTD)

Jeffrey A. Golvash, Golvash & Epstein, LLC, Pittsburgh, PA, for petitioner.
Ryan Daniel Pyles, U.S. Department of Justice, Washington, DC, for respondent.

DECISION DENYING ENTITLEMENT[1]

On October 28, 2016, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[2] alleging that the influenza ("flu") vaccine she received on November 8, 2013, caused her to suffer undifferentiated connective tissue disease ("UCTD"). (ECF No. 1, p. 1.) Petitioner later amended her petition to allege that she suffered significant aggravation of either Hashimoto's thyroiditis ("HT") and/or UCTD. (ECF No. 25, p. 2.) For the reasons set forth below, I conclude that petitioner is not entitled to compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 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 the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

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

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be "sound and reliable." *Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). The *Althen* court also indicated, however, that a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 481 F.3d at 1280.

Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a preexisting injury, petitioners must also establish three *additional* factors. *See Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part *Loving* test). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*. The Vaccine Act defines "significant aggravation" as a "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4).

In this case, petitioner alleges that the influenza vaccine she received on November 8, 2013, significantly aggravated her Hashimoto's thyroiditis ("HT") and/or undifferentiated connective tissue disease ("UCTD"). (ECF No. 25, p. 2.) Because neither of these injuries are listed as a Table Injury relative to the influenza vaccine, petitioner must satisfy the six-part *Loving* test.

II. Procedural History

Petitioner filed her petition *pro se* on October 28, 2016. (ECF No. 1.) This case was originally assigned to then Chief Special Master Dorsey. (*See* ECF No. 3.) Petitioner proceeded *pro se* while seeking representation, until September 8, 2017, when petitioner's counsel filed a motion to substitute attorney. (ECF No. 14.) After

petitioner secured representation, she filed medical records on January 16, 2018. (ECF Nos. 21, 22.) Thereafter, petitioner filed an amended petition on March 7, 2018, adding her significant aggravation claim. (ECF No. 25.) On March 29, 2018, respondent filed his Rule 4(c) Report recommending against compensation. (ECF No. 26.)

On October 4, 2018, petitioner filed updated medical records along with an expert report from rheumatologist Lige Rushing, M.D., M.S., P.A. (ECF No. 36.) Respondent filed a responsive expert report from rheumatologist Erin Wilfong, M.D., Ph.D., on March 5, 2019, and an additional report from immunologist Noel Rose, M.D., Ph.D., on May 6, 2019. (ECF Nos. 39, 43.)

This case was assigned to my docket on June 7, 2019. (ECF Nos. 49, 50.) Petitioner then filed a report from immunologist James DeAngelo, D.O., on October 7, 2019. (ECF No. 52.) Respondent filed responsive reports from Drs. Wilfong and Rose on December 20, 2019. (ECF No. 57.) Petitioner responded with two additional supplemental reports from Dr. DeAngelo on March 21, 2020 (one responding to Dr. Wilfong and one responding to Dr. Rose). (ECF No. 59.) Thereafter, the case was set for the scheduling of an entitlement hearing; however, respondent also filed a further report from Dr. Wilfong on July 13, 2020, and a further report from Dr. Rose on August 5, 2020. (ECF Nos. 65, 67.) On September 14, 2020, a two-day entitlement hearing was scheduled to commence on September 20, 2021. (ECF No. 70.)

However, on October 14, 2020, respondent advised that Dr. Rose had recently passed away. (ECF No. 71.) Respondent further indicated that he intended to retain an immunologist to testify at the hearing. (*Id.*) Thus, on November 19, 2020, respondent filed an additional expert report from immunologist Arnold Levinson, M.D. (ECF No. 72.) Petitioner filed a responsive report from Dr. DeAngelo on February 18, 2021. (ECF No. 75.) Respondent filed his final expert report from Dr. Levinson on June 3, 2021. (ECF No. 80.) On July 30, 2021, petitioner filed her final responsive expert report from Dr. DeAngelo. (ECF No. 86.)

A two-day entitlement hearing was held remotely on September 20th and 21st, 2021, via Webex. (*See* ECF Nos. 104-05, Transcript of Proceedings ("Tr."), filed 11/02/2021.) Petitioner testified and also presented testimony from her two experts, Drs. Rushing and DeAngelo. Respondent presented testimony from Drs. Wilfong and Levinson. This case is now ripe for resolution of entitlement.

III. Factual History

a. Medical Records

i. Pre-Vaccination Records

Petitioner's medical records document a history of mitral valve prolapse, lumbar laminectomy, gastroesophageal reflux disease ("GERD"), headaches, facial numbness,

Hashimoto's thyroiditis, sciatica, and vertigo. (Ex. 2, pp. 36, 41-42; Ex. 3, p. 6; Ex. 6, p. 95; Ex. 10, pp. 45, 64, 66-67; Ex. 12, p. 23; Ex. 13, p. 25.)

Upon experiencing vertigo, petitioner was examined by neurologist Dr. Jeffrey Farbman on June 26, 2013. (Ex. 6, pp. 94-96.) At a follow-up appointment on July 31, 2013, Dr. Farbman discovered petitioner's anti-nuclear antibody ("ANA")[3] positivity and referred her to a rheumatologist. (*Id.* at 91.) Petitioner's MRI revealed an abnormality, which was interpreted as potentially the result of migraine headache sequelae, minimal small vessel ischemic disease, a demyelinating disease, or vasculitis. (*Id.* at 90, 95.)

On August 15, 2013, petitioner presented to rheumatologist Dr. Kenneth Crane. (Ex. 10, pp. 40-44.) Petitioner reported a history of headaches, dizziness, Hashimoto's thyroiditis, and positive ANA. (*Id.* at 41.) Dr. Crane did not find any evidence to support a diagnosis of rheumatic disease and associated petitioner's positive ANA with her thyroiditis. (*Id.* at 44.) He noted left side facial numbness and the possibility of an inflammatory rheumatic disease. (*Id.* at 44, 48.)

On September 4, 2013, petitioner saw Dr. Crane in follow up for her positive ANA. (Ex. 10, p. 38.) Upon review of petitioner's labs, Dr. Crane noted positive anti-smith ("Sm") antibodies and ribonucleoprotein ("RNP") antibodies. (*Id.* at 38-39.) Based on these results, Dr. Crane suspected systemic lupus erythematosus ("SLE" or "lupus"). (*Id.*) He recommended repeat testing and a potential lumbar puncture if the results remained positive. (*Id.*)

On September 20, 2013, Dr. Crane noted that petitioner's follow up testing did not reveal Sm antibody positivity, but that she did maintain positive RNP antibodies. He wrote that positive ANA and RNP antibodies are commonly associated with connective tissue disease, though petitioner did not report any symptoms related to such a disease. Dr. Crane concluded that despite her elevated autoantibody levels, petitioner did not warrant further treatment. (Ex. 10, p. 34.)

Petitioner sought a second opinion from another rheumatologist, Dr. Glenn Wiener. (Ex. 3, p. 6.) On November 5, 2013, Dr. Wiener described his initial examination of petitioner in a letter to Dr. Glick. Dr. Wiener wrote that petitioner reported a history of chronic dizziness and lightheadedness over the previous four years, an episode of a severe headache with vertigo in June 2012, chronic headaches for the previous six years, tinnitus for several years, a meningioma of the brain, a mitral valve prolapse with palpitations and acid reflux, recent right-side neck pain, Hashimoto's

[3] "ANAs are used to diagnose autoimmune diseases, including systemic lupus erythematosus ("SLE"). Kathleen D. Pagana & Timothy J. Pagana, Mosby's Manual of Diagnostic and Laboratory Tests, ch. 2, at 80 (6th ed. 2018). ANA has fluorescent patterns in cells. *Id*. at 82. "Different patterns are associated with a variety of autoimmune disorders." *Id.* Mosby's states a positive ANA with a homogeneous pattern is associated with SLE and mixed connective tissue disease ("MCTD"). *Id.* It also says that a positive ANA with a speckled pattern is associated with SLE, scleroderma, RA, MCTD, Sjögren syndrome, and polymyositis ("PM"). *Id.* As for anti-RNP antibodies, they are associated with MCTD, SLE, and progressive systemic sclerosis (scleroderma). *Id.* at 81. MCTD is associated with ANA, anti-RNP antibodies, RF, and ssDNA. *Id.*

thyroiditis, and a lumbar laminectomy in 2001. (*Id*.) Dr. Wiener believed that petitioner's positive ANA "could be related to the recent diagnosis of autoimmune thyroid disease which is my suspicion." (*Id.* at 7.)

ii. Post-Vaccination Records

Petitioner received a flu vaccination in her left deltoid on November 8, 2013. (Ex. 1, p. 1.) On January 8, 2014, petitioner presented to Dr. Glick with a chief complaint of bilateral shoulder pain lasting six weeks. (Ex. 2, p. 9.) On January 22, 2014, petitioner returned to Dr. Glick for continuing pain / myalgias mostly in her upper arms. (*Id.* at 8.)

On February 5, 2014, Dr. Crane wrote to Dr. Glick explaining that he had seen petitioner that day for her shoulder pain which had improved significantly with a Medrol Dosepak. (Ex. 6, p. 61.) However, new laboratory studies had revealed leukopenia and Dr. Crane was concerned that petitioner may have SLE. (*Id.*) On February 19, 2014, Petitioner contacted Dr. Crane's office reporting increased pain in both arms. (Ex. 10, p. 26). She was started on prednisone. (*Id.*)

Petitioner next saw Dr. Crane on February 27, 2014. She reported continued upper arm and shoulder pain, a rash on her breast, and a mouth sore. (Ex. 10, p. 23.) Dr. Crane's impression was SLE, and he recommended Plaquenil and prednisone. (*Id.* at 25.) Petitioner remained on prednisone but refrained from taking Plaquenil due to potential side effects. (*Id.*)

A cervical MRI on March 5, 2014, showed a "[l]inear fluid signal in the central part of the spinal cord compatible with hydrosyringomyelia" and "[m]ild/moderate cervical spine degenerative changes." (Ex. 14, p. 8.)

On March 19, 2014, petitioner presented to hematologist Dr. Ronald Slade for consultation on using immunosuppressive therapy in the context of leukopenia. (Ex. 10, p. 78.) Dr. Slade felt that petitioner could continue using immunosuppressive therapy because her leukopenia was believed to be caused by her underlying autoimmune disorder. (*Id.* at 80.)

On March 20, 2014, petitioner presented to orthopedist Dr. Richard Rabinowitz for constant bilateral posterior neck pain lasting five months and radiating to her upper arms. (Ex. 9, p. 17.) Her physical examination was normal, and her MRI and x-ray were unremarkable. (*Id.* at 19.) Dr. Rabinowitz believed petitioner's pain was due to a degenerative disc and recommended physical therapy. (*Id.* at 20.)

On April 15, 2014, petitioner was evaluated by rheumatologist Dr. Rosalind Ramsey-Goldman who recorded the following medical history:

> Got a flu shot in 11/2013, ten days later developed myalgias in shoulders and upper arms. Took advil and tylenol without relief. Rheumatologist then recommended starting plaquenil, which she was nervous about starting because of possible vision side effects. Was started on prednisone . . .

> without improvement in shoulder/arm pain, but then did get relief with prednisone . . . which she has been taking for last 2 months. Muscle pain in shoulders and upper arms, with morning stiffness for 1 hour, pain worse at night. Now has pain in right forearm. Had repeat MRI of neck after shoulder symptoms started, was told she had an osteophyte on C5 (has discs with her but not report), unsure if causing symptoms. Has had low WBC counts in the past, ever since she was kid. Intermittent, spontaneously would be normal again. Normal differential. Saw a hematologist 10 years ago and no etiology found. [Patient] is also concerned because her total protein has increased on recent testing . . . . Had painful occipital lymphadenopathy in fall 2013 that resolved w/ medrol dosepak and antibiotics.

(Ex. 12, p. 23.) Petitioner also reported a "longstanding history of intermittent leukopenia" and recent development of pain in her right forearm. (*Id.* at 23, 28.) Dr. Ramsey-Goldman diagnosed petitioner with unspecified diffuse connective tissue disease ("UCTD"). (*Id.* at 29.) She planned to taper petitioner's steroids and monitor the response. (*Id.* at 28-29.)

On May 14, 2014, petitioner presented for a neurosurgery consult by Dr. Richard Broderick. (Ex. 14, pp. 2-4.) Dr. Broderick noted a medical history of bilateral shoulder / upper arm pain since November 2013 following petitioner's flu vaccination and positive ANA. (*Id.* at 2.) Petitioner reported that she experienced some relief of her joint pain when taking prednisone but noticed right wrist and hand pain when reducing her dosage. (*Id.*) Petitioner's brain and cervicothoracic MRI were unremarkable and not believed to contribute to her symptoms including her shoulder and wrist pain. (*Id.* at 4.)

On June 3, 2014, petitioner returned to Dr. Ramsey-Goldman to follow up on her joint pain and reevaluate her prednisone tapering. Dr. Ramsey-Goldman noted a history of Hashimoto's thyroiditis and suspected UCTD characterized by positive ANA and RNP, Raynaud's, steroid-responsive myalgia, arthralgia, and leukopenia. (Ex. 12, p. 22.) Petitioner reported increased joint and muscle discomfort while tapering prednisone in addition to third PIP[4] swelling and a rash on her knuckles. (*Id.* at 19.) Dr. Ramsey-Goldman recommended continued conservative treatment of petitioner's condition. (*Id.* at 22.)

Petitioner was discharged from physical therapy on June 19, 2014, after eighteen visits with pain with external rotation only and strength of 4/5. (Ex. 9, p. 21.)

On August 27, 2014, petitioner presented to Dr. Brooke Belcher for an orthopedic follow up for worsening carpal tunnel syndrome ("CTS") and a bilateral upper extremity EMG. (Ex. 9, p. 13.) Petitioner reported that her neck and arm pain was improving, but that her bilateral hand pain, numbness, and tingling had been getting worse. (*Id.*) Petitioner's EMG revealed a severe bilateral median mononeuropathy. (*Id.* at 29.)

[4] PIP or proximal interphalangeal joint is "the interphalangeal joint located proximally on any digit." *Proximal interphalangeal joint,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=83592 (last accessed July 26, 2022).

On September 3, 2014, petitioner presented to orthopedist Dr. Matthew Bernstein for an orthopedic follow up. (Ex. 9, p. 9.) Dr. Bernstein noted petitioner's history of Raynaud's and mixed connective tissue disease and that petitioner's CTS-related numbness and tingling began two months previously. (*Id.*)

On October 1, 2014, petitioner returned to Dr. Ramsey-Goldman's office for a rheumatology follow up. She reported that her fingers were puffy and that her rings did not fit. (Ex. 12, p. 12.) She also complained of worsening Raynaud's and occasional severe right knee pain. (*Id.*) The assessment was Raynaud's phenomenon, myalgia, arthralgia, and carpal tunnel syndrome, with UCTD suspected. (*Id.* at 17.) Dr. Ramsey-Goldman believed that petitioner Raynaud's symptoms could be exacerbated by a beta blocker she was on, and that she had a possible scleroderma. (*Id.* at 18.) Her recommended course of treatment was to continue wearing a splint and a trial course of diclofenac with possible carpal tunnel steroid injections. (*Id*.)

On December 31, 2014, petitioner returned to Dr. Ramsey-Goldman for a follow up. Dr. Ramsey-Goldman noted suspected UCTD characterized by positive ANA and RNP, steroid-responsive arthralgia and myalgia, Raynaud's, and intermittent leukopenia. (Ex. 12, pp. 5-6.) Dr. Ramsey-Goldman also noted petitioner's recent onset of bilateral carpal tunnel syndrome and her lack of response to steroid injections in November 2014. (*Id.* at 6.) Petitioner also reported swelling in her hands and fingers. (*Id.* at 6, 11.) Dr. Ramsey-Goldman reaffirmed petitioner's UCTD diagnosis with limited scleroderma. (*Id.* at 11.) Dr. Ramsey-Goldman recommended continued conservative treatment pending further evaluation of petitioner's scleroderma. (*Id.*)

Relative to her scleroderma concern, petitioner was evaluated by rheumatologist Dr. John Varga on March 18, 2015, and October 7, 2015. (Ex. 12, pp. 2-5.) Petitioner's history included diagnoses of Hashimoto's thyroiditis, UCTD, CTS, and Raynaud's. (*Id.* at 2, 4.) Petitioner also reported chronic fatigue and facial / trigeminal neuropathy. (*Id.* at 2-3.) Dr. Varga ruled out existing or developing proximal scleroderma. (*Id.* at 5.) Dr. Varga recommended that petitioner continue with prednisone as needed and follow up with rheumatology. (*Id*.)

On March 26, 2015, Petitioner saw Dr. Glick with new onset of discomfort and numbness on the left side of her face, including the tongue and lips. (Ex. 2, p. 3.) Dr. Glick prescribed a Medrol Dosepak, which offered some relief. (*Id*.)

In light of her new facial symptoms, petitioner returned to her neurologist, Dr. Farbman, on April 8th and 20th, 2015. (Ex. 6, pp. 84-87.) Petitioner's physical exam was significant for abnormal facial sensation in left V1 through V3 distributions. (*Id.*) Petitioner was prescribed Neurontin, which provided some relief. (*Id*.)

On May 4, 2015, petitioner presented to rheumatologist Dr. Sergey Furmanov, reporting symptoms of painful numbness on the left side of her face and tongue, swollen finger joints without pain, some hair loss, and Raynaud's phenomenon. (Ex. 10, p. 19.)

Dr. Furmanov noted that "UCTD seem[ed] to be the consensus," based on petitioner's prior rheumatology records. (*Id.*) He noted that petitioner's facial paresthesia "could be related to UCTD in the absence of another explanation." (*Id.* at 20.) Dr. Furmanov also noted that brain and spinal MRI revealed no evidence of demyelination and was therefore not contributing to petitioner's ongoing syndrome. (*Id.* at 16, 19.) Dr. Furmanov also noted evidence of PIP joint synovitis and Raynaud's. (*Id.* at 16-17, 18, 19-20.) Dr. Furmanov's concluded that petitioner's facial paresthesia was UCTD related. (*Id.*)

Petitioner was seen in follow-up by Dr. Furmanov on July 23, September 9, and November 18, 2015. (Ex. 10, pp. 4, 10, 13.) On November 18, 2015, Dr. Furmanov observed that petitioner's PIP joints were still slightly swollen but not tender; she had unchanged painful numbness on the left side of her face and tongue; her Raynaud's and mild hair loss were stable; and she awoke some nights with right knee pain that would subside spontaneously. (Ex. 17, p. 22.) Dr. Furmanov's assessment was: "1. UCTD/mild inflammatory arthropathy at PIP joints improved on HCQ, off Prednisone. 2. Facial paresthesia possibly related to UCTD. 3. Mild intermittent leukopenia, transaminitis are likely related to the inflammatory disease #1, stable. 4. Intermittent right knee pain." (*Id.* at 23.)

On January 4, 2016, petitioner was referred to Ronald Shade, M.D., for evaluation of her leukopenia, related to immunosuppressive therapy (Plaquenil) prescribed for her autoimmune disorder. (Ex. 61, p. 88.) Dr. Shade noted that petitioner had an undefined rheumatologic disorder and chronic mild leukopenia "which has remained stable for at least a decade." (*Id.*) He concluded that her mild leukopenia was due to her underlying autoimmune disorder and ordered her to continue follow-up management with her rheumatologist. (*Id.* at 90.)

On April 18, 2018, petitioner presented to Dr. Furmanov for a rheumatology follow-up reporting that she was "feeling good on HCQ 300 mg QD [without] PIP or other joint . . . pain/stiffness," and that her right knee was "OK." (Ex. 17, p. 1.) Her fatigue had not improved, her eyes and lips were a "little dry," though "no Raynaud's." (*Id.*) Petitioner was not participating in Zumba classes and was busy with school. (*Id.*) She reported that her left-side facial pain and numbness was stable on Neurontin and Xanax. (*Id.*) Dr. Furmanov documented substantially similar follow up exams of petitioner on October 11, 2018, May 29, 2019, October 10, 2019, April 15, 2020, and December 2, 2020. (*See* Ex. 60, pp. 2, 6, 12, 17, 22.)

b. Petitioner's Affidavit and Testimony

Petitioner filed an affidavit on August 9, 2021, describing the course and character of her alleged injury. (Ex. 64.) She notes a medical history of mitral valve prolapse, lumbar laminectomy, acid reflux, headaches, and Hashimoto's thyroiditis which was clinically stable due to prescribed Levothyroxine. (*Id.* at 1.) She states that she began experiencing bilateral upper arm and shoulder pain approximately 10 to 14

days after receiving her vaccination. (*Id.*) The pain was unlike any other she had felt before, was worse at night and interrupted her sleep. (*Id.*)

She explains that when the pain did not subside, she was seen by her primary care physician, Dr. Glick on January 8 and 22 of 2014. Her chief complaint was bilateral shoulder pain lasting six weeks and beginning approximately two weeks after her flu shot. (*Id.*) She was prescribed a Medrol pack and shoulder x-rays were taken and returned negative. Petitioner notes that the Medrol pack provided temporary relief but that her pain returned once she quit using the Medrol.

Petitioner explains that she was seen by her rheumatologist on February 5, 2014, due to her persistent joint pain and recent history of bilateral shoulder pain. She states that Dr. Crane suspected lupus and ordered additional bloodwork. She followed up with Dr. Crane on February 27, 2014, and reported that her pain syndrome had progressed to the midportion of her upper arms. She explains that she was told her pain could be caused by SLE or Sjogren's syndrome and was recommended treatment with Plaquenil and prednisone. Petitioner states that she started treating with prednisone but refrained from taking Plaquenil due to concerns over potential side effects. (Ex. 64, p. 1.)

Petitioner describes seeking a second opinion from rheumatologist Dr. Ramsey-Goldman on April 15, 2014. On this examination, petitioner explains that Dr. Ramsey-Goldman diagnosed her with UCTD based on her positive ANA and RNP, Raynaud's signs, and steroid-responsive arthralgia and myalgia. (Ex. 64, p. 2.) Petitioner affirms that joint swelling was not a condition that she had ever experienced prior to her flu vaccination. (*Id.*) Petitioner states that she was seen by Dr. Ramsey-Goldman on June 3, 2014, for a follow up on her UCTD. Petitioner had been tapering her prednisone use and reported that her pain increased as she decreased her dosage. Petitioner explains that the treatment plan was to continue tapering prednisone along with conservative treatment of petitioner's rheumatic disease. (*Id.*)

Petitioner explains that she was off prednisone by the time she was seen again by Dr. Ramsey-Goldman on October 1, 2014. (Ex. 64, p. 2.) She explained that she had new onset carpal tunnel syndrome and increased joint discomfort. She also reported new onset of swelling in her fingers and hands, and right knee discomfort. She was diagnosed with active rheumatic disease process with developing carpal tunnel. Petitioner notes that carpal tunnel was not a condition she experienced prior to her vaccination. (*Id.*)

Petitioner avers that she returned to Dr. Glick on March 26, 2015, with new development of numbness and discomfort on the left side of her face, including her tongue and lips. She was prescribed a Medrol dose pack, but it offered little relief. Petitioner reports that this was another condition that she did not experience prior to her vaccination. (Ex. 64, p. 2.)

Petitioner then explains that she was reevaluated by her neurologist, Dr. Farbman, on April 8th and 20th, 2015, for her new facial symptoms and ongoing joint

pain. Her physical exam noted abnormal facial sensation and she was prescribed Neurontin which provided some relief. Petitioner states that on June 19, 2015, she started Plaquenil due to her elevated liver enzymes and the suspicion of autoimmune hepatitis. (Ex. 64, p. 2.)

Petitioner sought further treatment for her facial paresthesia from her rheumatologist Dr. Furmanov on May 4th and June 25th, 2015. Her primary complaint was constant to moderate pain on her left side face along with swollen fingers and Raynaud's syndrome. She was advised to continue her Neurontin regimen. Dr. Furmanov associated her facial symptoms with her underlying UCTD. (Ex. 64, p. 3.)

Petitioner concludes her affidavit stating that while her rheumatic condition has improved over time, she continues to experience intermittent shoulder and upper arm discomfort, carpal tunnel, and finger and hand swelling. Her facial symptoms remain "fairly constant," and her daily living activities and recreational hobbies have been curtailed. She affirms that she believes her underlying UCTD was significantly aggravated by her flu vaccination, that she has suffered the symptoms of her condition for over six months, and that she has not received any compensation as a result of her injuries. (Ex. 64, p. 3.)

Petitioner's testimony during the hearing was largely consistent with her affidavit. (Tr. 6-45.) On cross examination, petitioner acknowledged that she had experienced facial numbness prior to her vaccination, in 2005, in 2011, and in 2013. (*Id.* at 40-41 (citing Ex. 10, pp. 48, 66; Ex. 9, p. 28.) However, she explained that it was a "totally different facial pain," she described "strange sensations . . . when I had headache . . . almost like a tiny little numbness." (Tr. at 41.) Petitioner testified, "It wasn't really a pain. And it could be on the left side or the right side." (*Id.* at 43.) She estimated that it occurred approximately once a year. (*Id.*) She explained that she mentioned the numbness during the MRI "in case it was significant" though it "wasn't really anything that bothered me. I just mentioned it in case it was somehow relevant to when I had a headache." (*Id.* at 44.) According to petitioner, Dr. Glick advised her that the facial numbness was a complication of her underlying headaches. (*Id.*) Petitioner testified that the onset of her headaches preceded vaccination, and the headaches occurred frequently enough to seek treatment, though it was "more of a remote history." (*Id.* at 42-43.) She testified that she did not experience a pattern of headaches post-vaccination. (*Id.* at 43.) Petitioner testified that the pain she currently has is significantly worse than any complaints of pain she may have had prior, in 2011 or 2015. (*Id.* at 45.)

IV. Summary of Experts' Opinions

a. For Petitioner

i. Lige B. Rushing, Jr., M.D., M.S., P.A.

Petitioner has offered Dr. Rushing as an expert in rheumatology and internal medicine.[5] Respondent does not object. (Tr. 53-54.)

Dr. Rushing concludes, accounting for petitioner's preexisting Hashimoto's thyroiditis and elevated ANA, it is likely that she experienced a vaccine-mediated reaction causing "arthralgia and myalgia, Raynaud's rash, hair loss, and facial paresthesia, and when coupled with positive ANA and RNP, led [petitioner's] treating rheumatologists to the post-vaccination consensus diagnosis of UCTD."[6] (Ex. 18, p. 5.) Dr. Rushing opines that the 10-to-14-day period of onset of petitioner's post-vaccination symptoms is within an appropriate medical timeframe to infer vaccine causation, and that the absence of any other causes shows that petitioner's vaccine is the necessary cause of her symptoms. (*Id.*)

Dr. Rushing agrees that petitioner's ANA and RNP bloodwork was representative of an underlying connective tissue disease that was subclinical at the time of her vaccination. (Tr. 65.) Dr. Rushing further indicates, however, that patients may be ANA and RNP positive for "years and perhaps their entire life without ever demonstrating or exhibiting clinical signs or symptoms of connective tissue disease." (*Id.* at 66.) Dr. Rushing opines that petitioner's asymptomatic connective tissue disease significantly worsened following her influenza vaccination on November 8, 2013. (*Id.* at 77.) Specifically, he observed that petitioner developed pain in her shoulders and arms, and subsequently developed Raynaud's. (*Id.*) Furthermore, she developed swelling in her hands and fingers, she had hair loss, and ultimately developed trigeminal neuropathy—"a whole new set of symptoms which she didn't have before the vaccine." (*Id.*)

Whereas respondent's experts discussed the possibility that petitioner's condition constitutes mixed connective tissue disease or "MCTD," Dr. Rushing opines that petitioner more likely suffers from UCTD. (Tr. 78-79.) According to Dr. Rushing, UCTD is a "recognized diagnosis," whereas mixed connective tissue disease is not. (*Id.* at 78.)

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[5] Dr. Rushing received his medical degree from Baylor University College of Medicine and completed his residency and internship in internal medicine at Harris Hospital in Fort Worth, Texas. (Ex. 19.) He held a fellowship in internal medicine and rheumatology at the Mayo Clinic in Rochester, Minnesota. He is certified by the American Board of Internal Medicine, the American Board of Geriatrics, and the American Board of Rheumatology. He has previously served as an affiliate physician at the Presbyterian Hospital of Dallas, Texas and is currently engaged in private practice of internal medicine and rheumatology. He is a member of the American Medical Association, the Texas Medical Association, the Dallas County Medical Association, and the Mayo Alumni Association. (*Id.*)

[6] Dr. Rushing also offers an alternative assessment that petitioner suffered polymyalgia rheumatica ("PMR"). (Ex. 18, p. 6.) However, respondent's experts disagreed (Ex. A, pp. 3-4; Ex. C, pp. 5-6) and petitioner ultimately did not rely on that assessment. Accordingly, PMR will not be addressed further.

MCTD typically involves a set of symptoms that do not confirm an identified rheumatic disease. In the case of UCTD, however, Dr. Rushing explains that "as the time goes by, they do differentiate into identifiable, recognized connective tissue disorders, such as scleroderma or lupus or rheumatoid arthritis." (*Id.*) Dr. Rushing also suggested that some rheumatologists may use these terms interchangeably, though he believes this is inaccurate. Petitioner, Dr. Rushing opines, more likely suffers from undifferentiated connective tissue disease because she did not exhibit enough signs or symptoms to fall under any one, or multiple, categories of connective tissue disease. (*Id.* at 79.)

Apart from petitioner having been administered an influenza vaccine, Dr. Rushing initially agreed that there was nothing unusual about petitioner's transition from subclinical to clinical connective tissue disease. (Tr. 101.) Asked whether, in his experience, physicians are able to identify an environmental trigger to the clinical presentation, Dr. Rushing testified "lots of times you cannot determine [the trigger]." (*Id.* at 101-02.) He testified that the medical literature on mixed connective tissue diseases suggests that "as high as 25 percent [of cases] you can't identify a trigger." (*Id*.) On redirect, however, Dr. Rushing suggested that the abruptness of petitioner's presentation from subclinical to clinical was an "unusual occurrence" in the context of a connective tissue disease that he has not seen in his own practice. (Tr. 104.)

Dr. Rushing's report also included a theory of vaccine causation based on the concept of "Autoimmune Syndrome Induced by Adjuvants" or "ASIA." (Ex. 18, p. 4 (citing Nabeela Siddiqi et al., *Polymyalgia Rheumatica and Autoimmune Inflammatory Syndrome Induced by Adjuvants Following Administration of Influenza Vaccine,* JCR 1 (2018) (Ex. 20); Alessandra Soriano et al., *Predicting Post-Vaccination Autoimmunity: Who Might Be at Risk?*, 92 PHARMACOL. RES. 18 (2015) (Ex. 21)).) However, he later opined during the hearing that ASIA syndrome is not relevant because petitioner's "vaccine didn't contain any adjuvants." (Tr. 89.) He agreed that his opinion "isn't predicated upon an ASIA analysis." (*Id.*) Instead, Dr. Rushing deferred to petitioner's immunology expert, Dr. DeAngelo, regarding the theory on vaccine causation. (*Id.* at 81, 89.)

ii. James N. DeAngelo, D.O.

Petitioner has offered Dr. DeAngelo as an expert in allergy and clinical immunology.[7] Respondent does not object. (Tr. 116-17.)

[7] Dr. DeAngelo received his medical degree from the Philadelphia College of Osteopathic Medicine, completed his internship in family medicine at Millcreek Community Hospital, his residency in internal medicine at West Virginia University in Morgantown, West Virginia, and a fellowship in allergy and immunology at the Cleveland Clinic Foundation in Cleveland, Ohio. (Ex. 24, p. 1.) He is licensed by the State of Pennsylvania. (*Id.* at 2.) He currently serves as Chair of the department of Allergy and Immunology at the Washington Hospital, and previously held positions as Director of the American Osteopathic Board of Allergy and Immunology, item writer for the Association of Clinical Research Professionals, Director of the Allergy and Immunology Subspecialty Board of the American Osteopathic Board of Internal Medicine, a Level III Item Writer for the Allergy and Immunology Section of the National Board of Osteopathic Medical Examiners, a Board Member of the American Osteopathic Board of Internal Medicine, Subspecialty Board Writer for Allergy and Immunology at the American Osteopathic Board of Internal Medicine, the District VIII Delegate for the Pennsylvania Osteopathic Medical Association's

Dr. DeAngelo acknowledges that petitioner showed signs of predisposition to autoimmunity prior to the vaccination at issue. (Ex. 42, p. 1.) However, he opines that the concept of "autoimmune tautology" explains how several co-existent autoimmune conditions can be found in the same individual, each with their own precipitant. (*Id*.) Dr. DeAngelo opines that "the environmental trigger for each autoimmune disease must be viewed independently of the overall predisposition to an autoinflammatory state." (*Id*. at 2.) In that regard, he stresses that petitioner was asymptomatic prior to her vaccination despite having elevated ANA and RNP antibodies and developed physical signs of connective tissue disease within two weeks of vaccination. (Ex. 62, p. 2.)

Dr. DeAngelo acknowledges that the vaccine at issue in this case did not contain an adjuvant and therefore petitioner's illness "does not strictly fulfill the original definition of ASIA, as described by Shoenfeld and Agmon-Levin in 2011." (Ex. 23, p. 1.) However, he suggests that it had many of the same characteristics, "suggesting a similar vaccine antigen-based pathogenesis as contemplated in subsequent ASIA medical literature." (*Id*.) Citing this ASIA literature, Dr. DeAngelo opines that exposure to the antigen within an inactivated flu vaccine can trigger the type of immune reactivity that has been linked to autoimmunity without exposure to live virus. (*Id.* at 10 (citing Yehuda Shoenfeld & Nancy Agmon-Levin, *'ASIA' – Autoimmunity/Inflammatory Syndrome Induced by Adjuvants*, 36 J. AUTOIMMUNITY 4 (2011) (Ex. C, Tab 2); Victoria Furer et al., *2019 Update of EULAR Recommendations for Vaccination in Adult Patients with Autoimmune Inflammatory Rheumatic Diseases*, ANN. RHEUM. DIS. 1 (2019) (Ex. 29); Siddiqi et al., *supra*, at Ex. 20; N. Toplak et al., *Autoimmune Response Following Annual Influenza Vaccination in 92 Apparently Healthy Adults*, 8 AUTOIMMUNITY REVIEWS 134 (2008) (Ex. 38); Abdulla Watad et al., *Seasonality and Autoimmune Diseases: The Contribution of the Four Seasons to the Mosaic of Autoimmunity*, 82 J. AUTOIMMUNITY 13 (2017) (Ex. 39); Abdulla Watad et al., *Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) Demonstrates Distinct Autoimmune and Autoinflammatory Disease Associations According to the Adjuvant Subtype: Insights from an Analysis of 500 Cases*, 203 CLIN. IMMUNOL. 1 (2019) (Ex. 40)).)

In the absence of an adjuvant, Dr. DeAngelo proposes that vaccine hemagglutinins, either alone or in combination with host proteins, can induce an autoinflammatory state. (Ex. 42, p. 3 (citing Maria Smatti et al., *Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms*, 11 VIRUSES 1 (2019) (Ex. 50); Timothy Z. Chang et al., *Host- and Pathogen-Derived Adjuvant Coatings on Protein Nanoparticle Vaccines*, 2 BIOENGIN. & TRANSLATIONAL MED. 120 (2017) (Ex. 46)).) He suggests that prior studies have shown increased levels of autoantibodies in people who receive flu vaccines. (Ex. 23, pp. 7-8 (K. Perdan-Pirkmajer et al., *Autoimmune Response Following Influenza Vaccination in Patients with Autoimmune Inflammatory Rheumatic Disease*, 21 LUPUS 175 (2012) (Ex. 32); Toplak et al., *supra*, at Ex. 38.)

House of Delegates, and as an intern delegate for western Pennsylvania to the Pennsylvania Osteopathic Medical Association's House of Delegates. (*Id.* at 2-3.) Dr. DeAngelo has also conducted 167 clinical research trials, 73 of which where he served as the primary investigator. (*Id.* at 3-17.)

Explaining his citation to ASIA further, Dr. DeAngelo explained that several proposed mechanisms may underlie the "broader ASIA umbrella." (Ex. 54, p. 2.) Specifically, he cites molecular mimicry, bystander activation, polyclonal activation, superantigen stimulation, and haptenization. (*Id*.) Ultimately, he explains that he is not relying on ASIA as "the mechanistic explanation" for petitioner's condition. (Ex. 62, p. 1.) Rather, he relies on ASIA as "a category of immune-mediated diseases that arise or worsen in a subset of genetically predisposed individuals . . . ." (*Id.*) That is, he cites ASIA as representative of what he opines occurred in this case, "antigens contained in the influenza vaccine set forth a cascade of events similar to what was originally described as ASIA and mediated through superantigen formation and epitope spreading." (*Id*.)

In his final report, Dr. DeAngelo introduced a study by Brauner et al., which also became a major focus of his testimony during the hearing. In Brauner et al., the authors found that individuals with preexisting connective tissue disease, specifically, Sjogren's syndrome, exhibited B-cell hyperactivity following H1N1 inoculation. (Ex. 62, pp. 2-3 (citing Susanna Brauner et al., *H1N1 Vaccination in Sjogren's Syndrome Triggers Polyclonal B Cell Activation and Promotes Autoantibody Production*, 76 ANN. RHEUM. DIS. 1755 (2017) (Ex. 63)).) This hyperactivity was "characterized by the overexpression of a variety of immune-related genes, including those downstream of the endosomal TLR signaling, and an enhanced capacity to undergo class switch and plasma cell differentiation when triggered by endosomal TLR ligands." (*Id.* at 3 (quoting Brauner et al., *supra*, at Ex. 63).) Dr. DeAngelo opines that the Brauner results show that untreated autoimmune patients are at a higher risk of autoimmune exacerbation when receiving the flu vaccine. (*Id.*) Dr. DeAngelo further opines that although petitioner was not diagnosed with Sjogren's syndrome, her condition is nonetheless a rheumatic disorder which causes systemic inflammation and autoimmune activation.[8] Thus, according to Dr. DeAngelo, "a solid immunologic and mechanistic parallel can be drawn in the context of [petitioner's] influenza vaccine and her untreated UCTD." (*Id.*)

During the hearing, Dr. DeAngelo provided detailed testimony regarding several figures contained within the Brauner paper (Figs. 2, 4, 5, and 6). (Tr. 163-83.) Dr. DeAngelo concludes that "Brauner's article[] basically suggest[s] that B cell function from untreated patients goes through the toll-like receptors, and that is basically supported by the fact that that response is aborted by the inhibition of the toll-like receptors with hydroxychloroquine." (Tr. 183.) Dr. DeAngelo stresses that "this doesn't happen in all untreated patients, but . . . not all of them go on to have . . . significant flares of autoimmunity but they could." (*Id.* at 184-85.) Brauner et al. shows "there's

[8] According to Dr. DeAngelo, there is significant overlap among connective tissue diseases. (Tr. 170.) He testified, "Again, we get back to this autoimmune typology where, you know, you have one common, you know, disease . . . autoimmune is equal to A is equal to B is equal to C." (*Id.*) However, he clarified that not all connective tissue diseases are comparable, but he confidently placed Sjogren's, dermatomyositis, polymyositis, mixed connective, undifferentiated connective, lupus, and possibly rheumatoid arthritis, all in the same category. (*Id.*) In contrast, others, such as Reiter's syndrome, ankylosing spondylitis, and psoriatic arthritis tend to form their own group. (*Id.*) Dr. DeAngelo did not offer any additional testimony regarding what characteristics or pathogenesis makes these diseases comparable or distinguishable. (*See id.*)

certainly an increase in polyclonal stimulation." (*Id.* at 185.) Over-stimulation creates a risk for the unmasking of an underlying condition or aggravation of an existing condition. (*Id.* at 187.)

Dr. DeAngelo furthermore explained that though Brauner involved the H1N1 seasonal flu vaccine, which is adjuvanted, petitioner "still would have responded one way or the other to the vaccine." (Tr. 191-92.) He opines that he "do[esn]'t see a difference really in response." (*Id.*) He further agreed that the authors of the Brauner study did not limit the application of the study to untreated patients with autoimmune rheumatic disease to the H1N1 Pandemrix vaccine. (*Id.* at 192-93.) Nowhere did the authors caution specifically against using an adjuvant. (*Id.*)

Drawing a logical sequence of cause and effect, Dr. DeAngelo testified that petitioner's influenza vaccine "introduced the foreign antigens to her body. She already had a hyper-excitable state." (Tr. 203.) Dr. DeAngelo infers that petitioner "had higher interferon alpha levels." (*Id.*) He testified that:

> All of the things that we saw in the Brauner study, she probably had all these. We don't have any evidence of that, of course, but she had a positive ANA at 1 to 320. She had a positive RNP. The antigen came into the body. The human body processed it, her antigen, in kind of a unique way. It may have been a unique antigen that year. The RNA and the hemagglutinins change every year when they make these viron vaccines. And we've seen this with other vaccines, where one year you have febrile seizures in children associated with a particular vaccine, and you don't see it in other years. So her body processed it in such a way that her body went through a process of probable molecular mimicry associated with bystander activation, epitope spreading, and then finally we saw the polyclonal B cell activation as part of this process, and presumably by inference, polyclonal T cell, but, I mean, I'm inferring that because the researchers didn't really look at that. And this was manifested in B cells that were clearly in the plasmablast category, and they were transitioning to plasma cells producing lots of antibodies, and I believe that those autoantibodies were autoantibodies, and I think that's largely responsible for some of her long-term consequences, but I also feel that the type I interferons were playing a very prominent role, as well as tumor necrosis factor and all of the other mediators of inflammation which were turned on by the immunization process.

(Tr. at 203-04.) Significant to Dr. DeAngelo's opinion was that there was no antecedent or precipitant event that would otherwise explain petitioner's significant worsening. (*Id.* at 204.) Dr. DeAngelo testified that there were no new medications introduced, no respiratory virus, no history of gastroenteritis, and no history of any other sort of infection prior to this. (*Id.*)

Seeking to establish a proximate temporal relationship between vaccination and injury, Dr. DeAngelo explained that Figure 1 in Brauner et al., shows a rise in the plasmablasts peaking at around ten days, and certainly within a fourteen-day timeframe. (Tr. 207-08; Brauner et al., *supra*, at Ex. 63, p. 1757, Fig. 1.) Specifically, he explained that it "take[s] a while for them to produce antibody, and then you see the concomitant rise in IgG levels, which is also that same time period, and we've already showed in [Figure 1E], we see the polyclonal stimulation is even more profound compared to the healthy controls, because you see that coming on around day ten. And, of course, it peaks much later, like at 45 days, but that would be expected." (*Id.* at 208.) In petitioner's case, Dr. DeAngelo notes that her symptoms and clinical indicators manifested within two weeks following her vaccination. He therefore concludes that onset of petitioner's rheumatic disease is consistent with the timeframe found in the Brauner study for anticipated/expected rise in antibody response and polyclonal activation of B cells following vaccination. (Ex. 62, p. 4.)

On cross-examination, Dr. DeAngelo acknowledged that "there's no way to say for certain what occurred. Something in the vaccine triggered the immune system, but I don't know what that something is in the Brauner article or in [petitioner's] case." (Tr. 212-13.) Dr. DeAngelo

> believe[s] that it is an antigen within the vaccine, and whether that vaccine had any homology, either after immune processing . . . [o]r it could have just simply been that she was responding to the vaccine itself and producing good antibodies to the influenza, but unfortunately, because she was so predisposed, she had an overreaching response, and began to respond to activate other already primed B cell clones. So [he] do[es]n't really know the exact process before the polyclonal activation.

(Tr. 213.) According to Dr. DeAngelo, vaccine hemagglutinins, either alone, or in combination with host proteins, are enough to induce an autoinflammatory state in a susceptible host. (Tr. 228 (quoting Ex. 42, p. 3).) Simply put, "there's two different ways," and Dr. DeAngelo cannot be sure which process occurred. (*Id.* at 230.) He explains that "nobody has done – and nobody would ever do . . . this basic bench research here, to try and find out which host protein." (*Id.*) He believes the hemagglutinin is a foreign antigen, and "as we've seen following vaccination in this susceptible population in the Brauner article, you see this rise of inflammatory mediators and antibodies. That means something's been recognized as bad. Whether that's the hemagglutinin or whether that's the hemagglutinin and a self-protein, [he] cannot say with any certainty." (*Id.* at 230-31.)

Going a step further, Dr. DeAngelo testified that he "believe[s] it could happen with any antigen, any foreign antigen, whether it's a natural infection or a component." (Tr. 233-34.) In fact, he opined, "It doesn't have to be flu. It could be – it doesn't have to be this strain. But different people respond differently to different strains and different antigens." (*Id.* at 234.) Dr. DeAngelo further agreed that any vaccine the CDC recommends for routine use in humans can precipitate or cause unmasking of an

asymptomatic connective tissue disease. (*Id.* at 234-35.) On cross examination, he agreed that any immunogenic protein from any virus or microbe can trigger a connective tissue disease, in individuals who are already prone. (*Id.* at 235.)

b. For Respondent[9]

i. Erin Wilfong, M.D., Ph.D.

Respondent has offered Dr. Wilfong as an expert in rheumatology.[10] Petitioner does not object. (Tr. 257.)

Dr. Wilfong suggests that the more likely diagnosis for petitioner's condition is mixed connective tissue disease. She explains that "[m]ixed connective tissue disease (MCTD) is characterized by the presence of high titer RNP antibodies, puffy fingers/swollen hands, Raynaud's phenomenon and synovitis (inflammatory arthritis)," and "myositis (muscle inflammation) is also commonly present." (Ex. A, p. 3.) Dr. Wilfong notes that petitioner had an elevated AST/ALT, which suggests mild myositis, exhibited puffy fingers, and was observed to suffer from synovitis.[11] (*Id.* at 4.)

Dr. Wilfong also explains that prior to her vaccination, there was already a concern that petitioner had an emerging connective tissue disease. (Ex. A, p. 5.) She notes that on June 26, 2013, petitioner was seen by her neurologist, complaining of vertigo. (*Id.* (citing Ex. 6, pp. 94-96.) The neurologist ordered an autoimmune workup to see if an autoimmune disease was contributing to her symptoms. Later, a letter to petitioner's neurologist from her rheumatologist stated that petitioner had positive Sm

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[9] As explained above, respondent presented three reports by Dr. Rose before his passing (Exs. C, I, and P) and then an additional two reports from Dr. Levison (Exs. Q and S), who succeeded him in this case and then ultimately testified at the hearing. Petitioner filed a total of five reports by Dr. DeAngelo (Exs. 23, 42, 43, 54, and 62) responding to all of these reports. Although Dr. Rose's reports remain a part of the record, his opinions will not be separately summarized given the availability of Dr. Levinson's opinion.

[10] Dr. Wilfong received her medical degree from Duke University School of Medicine in 2011. She completed her residency in internal medicine at Johns Hopkins Hospital in 2014, a rheumatology fellowship at the University of California, San Francisco in 2016, and is currently a Pulmonary & Critical Care fellow at Vanderbilt University. (Ex. B, p. 1.) Dr. Wilfong is certified by the American Board of Internal Medicine, and the American Board of Internal Medicine – Rheumatology. She is licensed to practice in California and Tennessee. (*Id.* at 2.) Dr. Wilfong has participated in six different clinical research studies and has published eight different pieces of medical literature on biochemistry and rheumatology. (*Id.* at 5.)

[11] Dr. Wilfong notes that there have been two sets of proposed diagnostic criteria for MCTD, but at the time of writing, neither had been accepted by the American College of Rheumatology. (Ex. A, p. 3.) The Alarcon-Segovia criteria are met if the patient shows an Anti-RNP at hemagglutination titer of greater than or equal to 1:1,600, and at least three symptoms including swollen hands, synovitis, myositis, Raynaud's phenomenon, and acrosclerosis – one of which must be synovitis or myositis. (*Id.* at 4, Table 1.) The Kahn criteria are met if the patient shows an RNP titer of greater than or equal to 1:1,200 and at least two of clinical presentations of either swollen fingers, synovitis, myositis, or Raynaud's phenomenon. (*Id.*) Dr. Wilfong explains that petitioner's RNP titer was at 214 AU/mL, which Dr. Wilfong opines satisfies both versions of the serologic criteria.

and RNP antibodies. (*Id.* (citing Ex. 6, p. 63.) The rheumatologist expressed concern that petitioner may be experiencing the early stages of SLE. (*Id.*)

According to Dr. Wilfong, during the preclinical phase in rheumatic disease, "genetic and environmental risk factors interact, probably sequentially, to initiate and propagate the development of autoimmunity, ultimately culminating in detectable tissue inflammation and injury. Furthermore, disease-related biomarkers, particularly autoantibodies, develop and evolve, initially in the absence of clinical signs and symptoms of tissue injury." (Ex. A, p. 4 (quoting Kevin Deane & Hani El-Gabalawy, *Pathogenesis and Prevention of Rheumatic Disease: Focus on Preclinical RA and SLE,* 10 NAT. REV. RHEUMATOL. 212 (2014) (Ex. A, Tab 3)).) Dr. Wilfong notes that studies of preclinical disease phases have most often been conducted on rheumatoid arthritis ("RA") and lupus ("SLE") patients. Five months preceding her diagnosis petitioner exhibited high RNP antibodies, which Dr. Wilfong opines places her in the preclinical phase of MCTD. (Ex. A, p. 5.) Thus, she concludes the vaccination did not cause the injury.[12] (*Id*. at 4.)

Dr. Wilfong's testimony was largely consistent with her expert reports. (Tr. 252-346.) Dr. Wilfong disagrees with petitioner's testimony that she developed all of her connective tissue disease symptoms post-vaccination. (*Id.* at 285.) Dr. Wilfong stresses, "She already had the antibodies. She already had arthralgia. She had morning stiffness noted. She had leukopenia prior to vaccination. Were these enough that I would have said to her in the office, You definitely have a connective tissue disease? No." (*Id.*) However, she stresses that petitioner's presentation was suggestive of an emerging CTD prior to vaccination. (*Id.*) Dr. Wilfong opines that petitioner showcased a "relatively typical progression." (*Id.* at 286.)

Specifically, Dr. Wilfong opined that petitioner began exhibiting symptoms of an emerging connective tissue disease in the summer of 2013. (Tr. 266.) She acknowledged that petitioner complained of arthralgias back in 2010, and while

[12] Dr. Wilfong cites several studies with respect to this discussion. In one RA study, 23% of patients had detectable autoantibodies at least 10 years prior to onset. (Ex. A, p. 4 (citing Jeremy Sokolove et al., *Autoantibody Epitope Spreading in the Pre-Clinical Phase Predicts Progression to Rheumatoid Arthritis,* 7 PLOS 1 (2012) (Ex. A, Tab 4)).). Over time, the level of autoantibodies rose until the patient eventually presented clinically. Another study found that the development of anti-CCP antibodies makes a patient 90% likely to develop clinical RA. (*Id.* (citing Deane & El-Gabalawy, *supra*, at Ex. A, Tab 3).) In an SLE study of 130 patients, 78% were found to have anti-nuclear antibodies up to 9.2 years preceding their diagnosis. (*Id.* at 5.) Positive ANA was on average detectable three years prior to diagnosis, and 79% of patients with an RNP component to their SLE showed detectable RNP antibodies as early as 7.2 years preceding diagnosis with an average detectability of .9 years preceding diagnosis. A longitudinal study by Frandsen et al., followed up on patients with high-titer anti-RNP antibodies. Only 56 out of 151 patients had been diagnosed with definitive connective tissue disease when the RNP antibodies were detected. (*Id.* (citing P.B. Frandsen et al., *Follow-Up of 151 Patients with High-Titer U1RNP Antibodies,* 15 CLIN. RHEUMATOL. 254 (1996) (Ex. A, Tab 5)).) By the end of the study, however, 127 patients had a definite connective tissue disease, and an additional 21 had probable connective tissue disease. On average, diagnosis was made 3.1 years after RNP antibody detection. (*Id.*) Dr. Wilfong uses these studies on preclinical disease phase to conclude that based on her autoantibody levels, it's likely that petitioner was in the preclinical phase of MCTD prior to her flu vaccination. (*Id.*)

arthralgia may indicate joint pain, it doesn't necessarily correspond to swelling and inflammation. (*Id.*) Dr. Wilfong observed that petitioner's headaches seemed to be progressing during the summer of 2013 and recalled mention of muscular or migraine headaches in February of 2013, and in March and during the summer. (*Id.* at 267.) She explained that 30 to 35 percent of patients with MCTD will develop vascular migraine headaches, compared to 12 percent of the general population or 18 percent of women.[13] (*Id.*)

By August 2013, petitioner reported morning stiffness. (Tr. 268-69.) Dr. Wilfong explains that morning stiffness is a diagnostic symptom for inflammatory arthritis—when "overnight as people aren't using their joints, their joints get stiffer, and in the morning, they're stiff for an hour or two, and the more they use their joints, the better they do." (*Id.* at 268.) The fact that morning stiffness was noted in Dr. Crane's notes, according to Dr. Wilfong, "is concerning that the [CTD] was definitely emerging by August of 2013." (*Id.* at 268-69.) At the same time, petitioner's RNP was found to be exceptionally high titer. (*Id.* at 269.) Dr. Wilfong explains that "this is the pathognomonic antibody for . . . mixed connective tissue disease, and so that's expected, given [petitioner's] ultimate clinical course, but, again, it's very concerning that we are really hearing the first true clinical obvious manifestation of her MCTD." (*Id.*) Although petitioner reported post-vaccination bilateral shoulder pain, Dr. Wilfong suggested that shoulder pain complicates CTD diagnosis. (*Id.* at 282.) She explained that it is a common complaint among patients, but may be caused by rotator cuff tendinopathy, for example, or myalgias or muscle pain which could be related to muscle enzymes subsequently being elevated in petitioner's mixed connective tissue disease. (*Id.*)

Dr. Wilfong further opines that there is no evidence that vaccinations exacerbate autoimmune rheumatic diseases. (Ex. A, p. 6.) Dr. Wilfong testified that for the influenza vaccine to act at the triggering event, the antigen should cross-react with the antibody of interest. (Tr. 302.) For connective tissue disease, the vaccine would either have to trigger a specific release of the RNP antigen from self in the circulation, leading to an increased amount of RNP antigen, or the influenza vaccine would need to have epitopic overlap with RNP. (*Id.*) Dr. Wilfong stresses, "I'm not aware of . . . evidence really supporting that." (*Id.*) In contrast, Dr. Wilfong cites several epidemiologic studies that she indicates show "there is substantial evidence that influenza vaccinations are safe and do not exacerbate systemic rheumatologic conditions." (Ex. A, p. 6; *see also* Tr. 297; Soriano et al., *supra*, at Ex. 21; Perdan-Pirkmajer et al., *supra*, at Ex. 32; Carla G.S. Saad et al., *Immunogenicity and Safety of the 2009 Non-Adjuvanted Influenza A/H1N1 Vaccine in a Large Cohort of Autoimmune Rheumatic Diseases*, 70 ANN. RHEUM. DIS. 1068 (2011) (Ex. A Tab 10); S. van Assen et al., *EULAR Recommendations for Vaccination in Adult Patients with Autoimmune Inflammatory Rheumatic Diseases,* 70 ANN. RHEUM. DIS. 414 (2011) (Ex. A, Tab 12); Mathilde Puges et al., *Immunogenicity and Impact on Disease Activity of Influenza and Pneumococcal*

[13] Dr. Wilfong further explained that trigeminal neuralgia is an inflammation of the sensory neuron of the trigeminal nerve—which is associated with MCTD, though the attack can last for weeks to months, and then abate completely for months to years. (Tr. 267.)

Vaccines in a Systemic Lupus Erythematosus: A Systematic Literature Review and Meta-Analysis, 55 RHEMATOL. 1664 (2016) (Ex. J); Zhengfa Liao et al., *Immunogenicity and Safety of Influenza Vaccination in Systemic Lupus Erythematosus Patients Compare with Healthy Controls: A Meta-Analysis,* PLOS ONE 1 (2016) (Ex. C, Tab 14).)

Turning to Brauner et al., Dr. Wilfong testified that the study is "not broadly generalizable." (Tr. 313.) Dr. Wilfong observed that the authors did in fact measure T cell frequency and found that there was no difference in the overall number of T cells, the frequency of CD4 or CD8 T cells, or activated T cells using CD62L as the marker. (*Id.* at 314.) She stressed that Brauner et al., found no differences in serum cytokines, such as interferon gamma, interleukin 4, or interleukin 17, in the sera of these patients. (*Id.*) Dr. Wilfong testified, that the figures in the Brauner article that Dr. DeAngelo relied upon showed elevated cytokines relative to the control, without statistical comparisons for the increase on day one, day ten, day 15, day 45, compared to zero. (*Id.* at 314-15.) Therefore, Dr. Wilfong challenges the idea that the study showed statistically different increases in cytokines, compared to the baseline for Sjogren's syndrome. (*Id.*) Dr. Wilfong also questions extrapolation of these results to vaccine efficacy "because there was actually no difference in any of the recorded clinical parameters, and the authors mention that caution is warranted in the abstract, but they don't actually discuss it anywhere in the discussion." (*Id.* at 315-16.) Dr. Wilfong also questioned the relevance of the Brauner article because, in her opinion, Sjogren's syndrome is not an appropriate model for B cell dysregulation with mixed connective tissue disease and RNP-positive disease. (Tr. 316.) She explained that B cell dysregulation is a hallmark in Sjogren's syndrome more than in any other CTD. (*Id.*)

In contrast, Dr. Wilfong cites Zhou et al., which showed that, in clinical trials of vaccination in Sjogren's patients compared to healthy controls, patients had higher antibody levels. (Tr. 317; Xingyu Zhou et al., *Immune Responses After Influenza Vaccination in Patients of Primary Sjogren's Syndrome,* 60 RHEUMATOLOGY 224 (2021) (Ex. W).) However, Dr. Wilfong testified that Zhou et al., did not find any difference in systemic adverse reactions, local injection site reactions, or changes in clinical or laboratory parameters in disease activity out to three months. (*Id.*) Ultimately, Dr. Wilfong stresses that Brauner et al. sought "to understand how B cells respond to vaccine[s] and conduct an in-detail, in vitro study evaluating the effects of B cells and linking the hyperactive state of B cells to proinflammatory cytokine exposures and changes in intracellular signaling proteins." (Tr. 318.) She concludes, "That was their stated goal, not vaccine safety." (*Id.*)

On cross examination, Dr. Wilfong testified Brauner et al. did not show any evolution of new autoantibodies. (Tr. 332.) Nor did the authors find any epitope spreading. (*Id.*) She stressed that polyclonal B cell activation alone does not correlate with disease activity. (*Id.* at 332-33.) She disagrees with the authors conclusion that "caution is warranted when considering vaccination in nontreated autoimmune patients." (*Id.* at 334.) Dr. Wilfong does not dispute the authors' finding of hypergammaglobulinemia as well as polyclonal B cell activation. (*Id.* at 344-45.) Even still, Dr. Wilfong stresses that Brauner et al. used an adjuvanted vaccine. (*Id.*)

ii. Arnold I. Levinson, M.D.

Respondent has offered Dr. Levison as an expert in immunology.[14] Petitioner does not object. (Tr. 356-57.)

As a threshold issue, Dr. Levinson opines that the ASIA concept is not very useful and that it "tell[s] us nothing about a causal relationship between vaccine administration and the disorders that have been reported to the Shoenfeld ASIA registry, including MCTD." (Ex. Q, pp. 4-5.) As the name implies, "the supposed unifying construct" of ASIA is that siliconosis, gulf war syndrome, MMF and other "post-vaccination phenomena" are all caused by the "untoward actions of adjuvants on the immune system."[15] (*Id*.) Dr. Levinson explains that acceptance of ASIA has waned over time because it uses an "extremely nonspecific description of clinical features and [a] very loose definition of the temporal relationship between alleged adjuvant exposure and onset of disease manifestations." (*Id.* at 4.) He notes that recent publications have challenged the soundness and the utility of these concepts, based "largely on the lack of specificity of the disorder's diagnostic criteria and the imprecisely described temporal relationship between vaccine exposure and onset of symptoms." (*Id.* (citing David Hawkes et al., *Revisiting Adverse Reactions to Vaccines: A Critical Appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA)*, 59 J. AUTOIMMUNITY 77 (2015) (Ex. C, Tab 12); Rohan Ameratunga et al., *Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA)*, 5 J. ALLERGY. CLIN. IMMUNOL. PRACT. 1551 (2017) (Ex. C, Tab 9)).) He notes that critics have argued that the ASIA diagnostic criteria "would likely encompass all patients with any autoimmune disorder as well as a large proportion of the general population who have the prescribed non-specific symptoms." (*Id.*) Importantly, Dr. Levinson stresses that ASIA has not been defined by an underlying biological mechanism, and therefore,

[14] Dr. Levinson received his medical degree from the University of Maryland in 1969, completed his internship in internal medicine at Baltimore City Hospital in 1970, and has held fellowships in immunobiology, immunology, and allergy at Johns Hopkins Hospital, the University of Pennsylvania School of Medicine, and the University of California, San Francisco Medical Center. (Ex. R, p. 1.) Dr. Levinson has served as an assistant professor of medicine and pediatrics at the Uniformed Services University of Health Sciences, as an associate professor of medicine and neurology at the University of Pennsylvania School of Medicine, as a full professor of Medicine and Neurology at the University of Pennsylvania, as associate dean for research at the University of Pennsylvania School of Medicine, and now as an emeritus professor of medicine and neurology. (Ex. R, p. 1.) He is certified by the American Board of Internal Medicine and the American Board of Allergy and Clinical Immunology and licensed by the state of Pennsylvania. (*Id.* at 2.) Dr. Levinson has served as editor for the Journal of Allergy and Clinical Immunology and the Journal of Clinical Immunology. (*Id.* at 4.) He has also published 46 pieces of peer-reviewed medical literature on allergy, immunology, and neurology. (*Id.* at 18-21.)

[15] Dr. Levinson clarifies that adjuvants are "considered by immunologists to be agents that boost specific T and B cell immune responses to co-administered antigens." (Ex. Q, p. 4.) Adjuvants boost the immune response by "directly stimulating innate immune responses, which subsequently promote the development of antigen-specific adaptive . . . responses in the lymph nodes that drain the site of antigen/adjuvant exposure." (*Id.*) The most commonly used adjuvants in vaccines approved for administration in the United States are aluminum salts. However, as Dr. DeAngelo likewise acknowledges, Dr. Levinson stresses that petitioner's vaccination did not contain any adjuvants. (*Id.*)

including it as a clinical entity "provides no clear exposition of the biologic processes responsible for the pathogenesis of [ASIA]." (*Id.* at 4-5.)

Dr. Levinson explains that the literature Dr. DeAngelo relies on to show an association between autoimmune disease and the flu vaccine are simply temporal associations but do not find a causal link. (Ex. Q, p. 6.) Additionally, Dr. DeAngelo "further muddies the water by saying that the medical literature he discussed actually indicates that flu vaccination with adjuvanted or unadjuvanted vaccines induces more frequent and 'severe reactions' in patients with autoimmune disease." (*Id.*) Dr. Levinson explains that if Dr. DeAngelo is suggesting that the vaccines exacerbate clinical autoimmune disease, he has misinterpreted the literature because there is "absolutely no epidemiological data that support his contention," and that if this were true, the European League Against Rheumatism ("EULAR") would not recommend administration of the flu vaccine to patients with rheumatic disease. (*Id.*)

Dr. Levinson questions why Dr. DeAngelo raised the concept of autoimmune tautology because there is no disagreement that petitioner suffered from more than one autoimmune disease, specifically Hashimoto's thyroiditis and MCTD. (Ex. Q, p. 6.) According to Dr. Levinson, this concept does not shed any light on the medical theory, logical sequence of cause and effect, or accepted timing of onset linking the flu vaccine to MCTD. (*Id.*) Dr. Levinson also notes that Dr. DeAngelo's reliance on literature regarding monogenic autoinflammatory diseases is misguided because "these disorders are pathogenically quite different from the polygenic autoimmune disorders," that petitioner suffered from. (*Id.* at 7.)

Dr. Levinson is critical of Dr. DeAngelo's reliance on studies by Smatti et al., and Chang et al., to demonstrate that vaccine hemagglutinins can produce an autoinflammatory state without any adjuvant. (Ex. Q, p. 7.) According to Dr. Levinson, Smatti et al., examined live viral infections, rendering comparison to vaccination as false equivalency given that viruses replicate in vivo, thereby augmenting the magnitude of the viral antigen encountered. (*Id.*) Smatti et al. did examine two inactivated flu vaccines (Pandemrix and Focetria), both adjuvanted, which is counter to Dr. DeAngelo's reliance on the paper. (*Id.*) Chang et al. dealt with the mechanisms by which IgM coated ovalbumin-modified nanoparticles enhanced the immune response of mice to ovalbumin. Dr. Levinson explains that this is a very specialized experiment model that deals with a solid phase antigen which measured the immune response to the antigen, and not the induction of an autoimmune response. (*Id.*) Thus, according to Dr. Levinson, none of the literature cited by Dr. DeAngelo shows how an inactivated, adjuvant-free soluble flu antigens can "somehow be adjuvanted by a host protein and give rise to an autoimmune response." (*Id.* at 8.)

Dr. Levinson's testimony was largely consistent with the opinions expressed in his expert reports. (Tr. 349-408.) Generally speaking, Dr. Levinson testified that molecular mimicry is a term that refers to "sharing of antigenic determinates or what we call epitopes, particularly molecular epitopes or motifs on exogenous antigens and self antigens." (Tr. 361.) In the abstract, molecular mimicry involves the sharing of

epitopes. (*Id.*) However, Dr. Levinson testified that most proposed cases of molecular mimicry do not translate into clinical tissue destruction. (*Id.* at 361-62.) Despite proof that there is epitope sharing on an exogenous antigen and a self-antigen, other features must be present "in terms of licensing or weaponizing that abstract molecular mimicry." (*Id.* at 362.) The other features include antigen presentation, profound tissue inflammatory milieu, quantitative and qualitative features of T cells or B cells that engage in an inflammatory reaction. (*Id.*) Dr. Levinson stresses that we must consider the status or integrity of the immunoregulatory mechanisms that are in place to suppress this type of reactivity that might occur as a response to molecular mimicry. (*Id.)*

With respect to Brauner et al., Dr. Levinson stresses that the study again involved an adjuvanted H1N1 vaccine. (Tr. 370-71.) Furthermore, the adjuvant at issue is AS03, an adjuvant system containing squalene, alpha-tocopherol, polysorbate 80. (*Id.*) Squalene, he explains, is a component of shark tincture, while alpha-tocopherol is an "iso form of vitamin E," which is immune-stimulating, and polysorbate 80 is an emulsifying agent. (*Id.*) Dr. Levinson suggests that this is a powerful adjuvant that markedly increases antigen uptake and presentation in the draining lymph node, particularly when it's administered as part of a vaccine. (*Id.* at 371.) He explains that AS03 stimulates powerful B and T cells—creating a much higher magnitude of antibody response. (*Id.*) Importantly, there was no control for this adjuvant in Brauner et al. (*Id.* at 371-72.) Additionally, Dr. Levison notes that Brauner et. al. offers no evidence of exacerbation of underlying disease, i.e., Sjogren's syndrome, or the nonspecific symptoms of rheumatic autoimmune disease (other than fever). (*Id.* at 374.)

Subsequent to the Brauner article, Zhou et al., studied patients with Sjogren's syndrome to determine if, in fact, immunization with a flu vaccine, this time, unadjuvanted seasonal H1N1 flu vaccine, affected immune parameters and whether the vaccine led to an exacerbation of clinical disease. (Tr. 376.) Dr. Levinson emphasized the fact that Zhou et al. used established disease activity indices to study patients at baseline and as late as three months post-vaccination. (*Id.*) The authors observed some changes in T cell subsets, post-vaccination. (*Id.*) Notably, they did not see the kinds of results seen in the earlier Brauner study, with regard to the B cell activation. (*Id.*) In particular, Dr. Levinson observed that Zhou et al., did not see increased numbers of plasmablasts or memory B cells in among the patients. (*Id.* at 377.) Nor did they see evidence of polyclonal B cell activation in the patients' serum. (*Id.*) As Dr. DeAngelo testified, on occasion results in these studies will show evidence of the activation of the complement system, and C3 and C4 will "sometimes go down." (*Id.*) In Zhou et al., however, no such results were found. On cross examination, Dr. Levinson acknowledged that Zhou et al. did not differentiate between patients who were treated with immunotherapy versus those that were not—which he explained is a shortcoming of the study. (Tr. 394.) In response, Dr. Levinson stressed that Zhou et al. conducted the study in response to the Brauner study. (*Id.*) He stressed that the authors focused on cellular activation in vitro. (*Id.*)

V. Discussion

a. Diagnosis

Petitioner's experts opine that petitioner more likely than not suffers from UCTD. (Tr. 78-79.) In his prehearing brief, respondent concurs that more likely than not, petitioner's diagnosis includes a connective tissue disease. (ECF No. 96, p. 15.) However, respondent's experts favor a diagnosis of MCTD. (Ex. A, p. 7; Ex. Q, p. 2; Tr. 257-66.)[16] Yet, as Dr. Levinson observes, "the terms MCTD and UCTD are often used interchangeably to diagnose an autoimmune rheumatic condition that fails to meet the criteria of a distinct condition such as systemic lupus erythematosus or polymyositis." (Ex. Q, p. 2). Furthermore, Dr. Wilfong testified that, "this is an argument of semantics, whether we're going by classification criteria [or] diagnostic criteria . . . [h]er clinical symptoms are the same and . . . how exactly we classify or diagnose her is really irrelevant to causation or her clinical course." (Tr. 265-66.)

Thus, based on my review of the relevant medical literature and expert opinions in this case, it is not necessary to parse whether petitioner's condition is better characterized as UCTD or MCTD. Although petitioner must specify her injury and shoulder the burden on causation, the function of a special master is not to 'diagnose' vaccine-related injuries. *See Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1382 (Fed. Cir. 2009); *Stillwell v. Sec'y of Health & Human Servs.*, 118 Fed. Cl. 47, 56 (2014); 42.U.S.C. § 300aa-11(c). Given that the diagnosis stated by petitioner's treating rheumatologists was UCTD and given Dr. Wilfong's testimony that "how exactly we classify or diagnose [petitioner] is really irrelevant to causation," the causation-in-fact analysis will be addressed in the context of UCTD. (Tr. 266.)

b. Petitioner's Medical Theory (i.e., *Althen* Prong One / *Loving* Prong Four)

The most extensively debated aspect of this case is the validity of petitioner's theory of causation explaining how petitioner's flu vaccination could have significantly aggravated her condition. This presents a threshold issue in this case. Accordingly, I will address petitioner's theory of causation first. Having found that petitioner did not meet her burden of proof on this point, I will then more briefly address the remaining elements of the six-part *Loving* test discussed above.

Petitioner's burden under the first *Althen* prong / fourth *Loving* prong is to provide, by preponderant evidence, "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners in the Vaccine Program are not charged with demonstrating the "exact process" or precise mechanism underlying their alleged vaccine injury. *Kottenstette v. Sec'y of Health & Human Servs.*, 861 F. App'x 433, 441 (Fed. Cir. 2021); *Knudsen*, 35 F.3d at 548. Moreover, scientific

[16] Dr. Rose suggested a differential diagnosis of UCTD or MCTD. (Ex. C, p. 8.)

evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs*., 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, to satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548; *Boatmon*, 941 F.3d at 1359.

As explained above, much of the discussion within the experts' reports focused on the ASIA concept. Dr. DeAngelo explained that several proposed mechanisms may underlie the "broader ASIA umbrella," citing mechanisms such as molecular mimicry,[17] bystander activation, polyclonal activation, superantigen stimulation,[18] and haptenization. (Ex. 54, p. 2.) Ultimately, however, he explains that he is not relying on ASIA as "the mechanistic explanation" for petitioner's condition. Rather, he relies on ASIA as "a category of immune-mediated disease that arise or worsen in a subset of genetically predisposed individuals." (Ex. 62, p. 1.)

[17] Though molecular mimicry is a generally accepted scientific concept, and is frequently invoked in Vaccine Program cases, mere mention of this theory does not constitute a preponderant showing. *McKown v. Sec'y of Health & Human Servs*., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (stating 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 in question"). In his reports, Dr. DeAngelo did initially purport to demonstrate molecular mimicry by citations to studies by Borba et al. and Shah et al. (*See*, *e.g.*, Ex. 54, p. 6.) Because he ultimately testified that he cannot rely on molecular mimicry, it is not necessary to address this at length. However, I note that Dr. DeAngelo's reliance on these two studies is unpersuasive. Borba et al. focuses on sarcoidosis, Sjogren's syndrome, UCTD, and silicone implant incompatibility as classic examples of ASIA. (Vania Borba et al., *Classic Examples of the Concept of the ASIA Syndrome*, 10 BIOMOLECULES 1 (2020) (Ex. 56).) ASIA is addressed separately below; however, Dr. DeAngelo fails to explain how this study supports molecular mimicry between components of the flu vaccine and any tissue implicated in UCTD. Shah et al. suggested that SARS-CoV-2 infection can potentially lead to an array of rheumatological and autoimmune manifestations via molecular mimicry, "bystander killing," epitope spreading, viral persistence and formation of neutrophil extracellular traps. (Sanket Shah et al., *Autoimmune and Rheumatic Musculoskeletal Diseases as a Consequence of SARS-CoV-2 Infection and Its Treatment*, 40 RHEUMATOL. INT'L. 1539 (2020) (Ex. 58).) Dr. Levinson, however, explains that "[t]here is no evidence presented that the supposed mimicking SARs CoV-2 epitopes function as T or B cell immunogenic epitopes." (Ex. S, p. 3.) Furthermore, there is no evidence presented "that any of the cross-reactive sequences on human proteins actually represent immunogenic epitopes and, more importantly, are the targets of an adaptive immune attack as a consequence of SARs CoV-2 infection." (*Id.*)

[18] Dr. DeAngelo also proposed superantigen formation as another possible cause for polyclonal activation in this case. (Tr. 241.) In response, Dr. Wilfong testified that superantigen formation is not a reliable theory of causation to establish that the flu vaccine more likely than not can cause connective tissue disease or a similar rheumatic autoimmune disease. (*Id.* at 378.) According to Dr. Wilfong, superantigens "turn on a load of T cells, in the case of a T cell superantigen, or B cells, in the case of a B cell superantigen." (*Id.* at 379.) According to Dr. Wilfong, the antigens that are present in a seasonal influenza flu vaccine are conventional antigens. (*Id.*) Specifically, she testified that "I'm not aware of any evidence that a viral flu hemagglutinin or neuraminidase has any kind of superantigen potential, so I don't see how [Dr. DeAngelo] go[es] from flu vaccine antigen to superantigen activity in vivo." (*Id.* at 379-80.) Superantigens, according to Dr. Wilfong, induce roughly 60 percent of T cells or 30-60 percent of B cells. (*Id.* at 379.) In contrast, conventional antigens induce only .0001 or one in 10,000, T cells. (*Id.*)

Thus, Dr. DeAngelo ultimately opined that his theory relies on polyclonal activation, further explaining that "you have to have some sort of stimulus. And you have to have an antigenic stimulation to get polyclonal activation." (Tr. 212.) He indicated that other possible mechanisms that occur before polyclonal stimulation include epitope spreading and molecular mimicry. (*Id.*) However, he testified that "the only one I can confirm is that from the literature that I've reviewed is that there's definitely evidence here from the Brauner article that, at least in Sjogren's syndrome and by inference other connective tissue disease, that you see polyclonal activation." (*Id.*) Dr. DeAngelo explained that "there's no way to say for certain what occurred. Something in the vaccine triggered the immune system, but I don't know what that something is in the Brauner article or in [petitioner's] case." (Tr. 212-13.) According to Dr. DeAngelo, "because [petitioner] was so predisposed, she had an overreaching response, and began to respond to activate other already primed B cell clones" though he admitted, "I don't really know the exact process before the polyclonal activation." (*Id.* at 213.)

Examining this theory of causation requires several separate discussions. First, the analysis below addresses whether Dr. DeAngelo is persuasive in relying on the above-referenced Brauner article to evidence polyclonal B cell activation occurring in the context of this vaccine and injury. Second, a subsequent analysis addresses by what basis Dr. DeAngelo suggests that the flu vaccine can act as the antigenic stimulant that he indicates is necessary to begin that process. Finding that Dr. DeAngelo is not persuasive on either point, the third and final analysis examines whether Dr. DeAngelo is persuasive in invoking ASIA "as a category of immune-mediated disease" to nonetheless support vaccine-causation as a matter of epidemiology.

1. Polyclonal B Cell Activation

Dr. DeAngelo opines that "[a]utoimmune diseases such as UCTD are believed to be the result of aberrant B and T cell dysfunction directed against self-antigens." (Ex. 23, p. 10 (citing Watad et al., *supra*, at Ex. 40).) In that regard, he opines that petitioner's alleged vaccine-injury resulted from polyclonal B cell activation. (Tr. 212-13.) As noted above, Dr. DeAngelo sought to draw support for this mechanism primarily from a study by Brauner et al. (Tr. 163-200; Brauner et al., *supra*, at Ex. 63.) Brauner et al., found that individuals with preexisting connective tissue disease, specifically Sjogren's syndrome, exhibited B-cell hyperactivity following H1N1 vaccination. (Brauner et al., *supra*, at Ex. 63.) This hyperactivity was "characterised by the overexpression of a variety of immune-related genes, including those downstream of the endosomal TLR signaling" with an enhanced capacity to undergo class switching and plasma cell differentiation when triggered by endosomal TLR ligands. (*Id.* at 1758.) Dr. DeAngelo opines that these results show that untreated autoimmune patients are at a higher risk of autoimmune exacerbation when receiving the flu vaccine. (Ex. 62, p. 3.)

However, Brauner et al. acknowledge that the symptoms in Sjogren's patients in their study did not correspond or correlate to their B cell findings. Despite the markedly increased B cell responses observed in the Sjogren's patients, Brauner et al. "noted no

significant differences between patients and controls with regard to the recorded clinical parameters fever, fatigue, myalgia and arthralgia." (Brauner et al., *supra*, at Ex. 63, p. 1762.) These manifestations, according to the authors, "represent common symptoms of both Sjogren's syndrome and adverse reactions to vaccination." (*Id.*) Notably, however, similar frequencies of affected individuals were observed after vaccination in both groups. (*Id.*) In his testimony, Dr. DeAngelo suggested that the only symptom that showed a significant increase was the frequency of fever. (Tr. 157.) According to Dr. DeAngelo, the study finding regarding disease activity (depicted at Figure 2) is "kind of irrelevant, simply because it's looking at symptoms that would be associated with like lupus or mixed connective tissue disease" while Sjogren's patients typically suffer dry eyes and dry mouth, exocrine dysfunction in the pancreas or lungs, or even respiratory symptoms. (*Id.* at 165.) However, Brauner et al. explained that they monitored "common clinical signs of disease activity" which included fever, fatigue, myalgia, and arthralgia, parameters which are now part of the Sjogren's syndrome disease activity scores (known as ESSPRI and ESSDAI). (Brauner et al., *supra*, at Ex. 63, p. 1756.) Despite Dr. DeAngelo's criticism that these symptoms are irrelevant to Sjogren's syndrome, Brauner et al. confirmed that these symptoms are indeed part of the Sjogren's syndrome disease activity scores. Therefore, the fact that Brauner et al. noted no significant difference between patients and controls with regard to the clinical parameters is significant and undercuts the authors own caution against vaccination.

Additionally, studies conducted both before and after Brauner further confirm that post-vaccination findings have not been pathogenic. The Brauner authors report, "[i]n contrast to previous studies reporting less vigorous immune responses to vaccination in patients with autoimmune rheumatic disease, we found that untreated patients with autoimmune [primary Sjogren's syndrome] developed higher levels of vaccine-specific IgG antibodies than matched controls." (Brauner et al., *supra*, at Ex. 63, p. 1762.) In one of the prior studies, in 2006 Holvast et al., measured antibody titers against influenza viruses in patients with quiescent lupus 30 days post influenza vaccination. (A Holvast et al., *Safety and Efficacy of Influenza Vaccination in Systemic Lupus Erythematosus Patients with Quiescent Disease*, 60 RHEMATOL. 224 (2021) (Ex. V).) The authors included four patient groups: (1) no drug treatment; (2) hydroxychloroquine treatment; (3) azathioprine treatment; and (4) prednisone treatment. (*Id.* at 913.) The patients were vaccinated with Influvac, a subunit vaccine in October and November 2003. (*Id.* at 914.) Sera of the patients was tested against three vaccine strains, H3N2, A/H1N1, and B/Hong Kong. (*Id.*) Results (shown in Figure 1) using the validated disease activity indexes ("SLEDAI scores") showed no evidence of disease exacerbation or increase in patient perception of disease activity. (*Id.* at 916.) These results, according to Holvast et al., are consistent with previous studies in which clinical- and laboratory-assessed lupus disease activity did not increase post-vaccination. (*Id.*) Overall, Holvast et al., stress that influenza vaccination is safe in SLE patients.

In direct response to Brauner's study, Zhou et al. designed a study to monitor clinical features and serological responses in patients with primary Sjogren's syndrome who received China's domestic quadrivalent influenza vaccine, a live attenuated vaccine containing H1N1, H3N2, and the Yamagata lineage. (Zhou et al., *supra*, at Ex.

W, p. 225.) Zhou et al.'s results demonstrated that Sjogren's patients developed higher levels of vaccine-specific IgG antibodies than the healthy controls, consistent with Brauner et al. (*Id.* at 226-28.) Importantly, however, the robust immune responses to vaccination "[were] not accompanied by an increase in disease-specific serological immune responses." (*Id.*) Moreover, influenza vaccination did not aggravate disease severity or any other significant adverse effects.[19] (*Id.*)

Further to this, Dr. Levison raised the use of an adjuvanted H1N1 vaccine as a significant limitation in the Brauner study. (Tr. 370.) He stresses that the H1N1 vaccine examined in Brauner was adjuvanted with AS03, an adjuvant system containing squalene, alpha-tocopherol, polysorbate 80. (*Id.* at 370-71.) Squalene, he explains, is a component of shark tincture; while alpha-tocopherol is an "iso form of vitamin E" which is in and of itself immune-stimulating, and polysorbate 80 as an emulsifying agent. (*Id.*) Taken together, Dr. Levinson stresses that this is a powerful adjuvant that markedly increases antigen uptake and presentation in the draining lymph node, particularly when it's administered as part of a vaccine. (*Id.* at 371.) He explains that AS03 stimulates powerful B and T cells—creating a much higher magnitude of antibody response. (*Id.*) Importantly, Dr. Levinson stresses that there was no control for this adjuvant in Brauner et al. (*Id.* at 371-72.)

Moreover, the authors themselves discuss additional reasons that their hypothesis is tied to the specific vaccine formulation they studied, the 2009 pandemic split vaccine – which suggests that their results may not be generally applicable, as Dr. DeAngelo suggests. (Brauner et al., *supra*, at Ex. 63, p. 1762.) Brauner et al. acknowledge that "[i]t is therefore possible that RNA present in the split-virus Pandemrix vaccine used in our study may contribute to the increased plasma cell differentiation and antibody production detected in patients by stimulating patients by stimulating B cell endosomal TLRs."[20] (*Id.*)

In light of all of the above, Dr. DeAngelo's reliance on Brauner et al. is unpersuasive.

2. Hemagglutinin

As explained above, Dr. DeAngelo acknowledges that he is unable to explain what process precedes the polyclonal activation he posits; however, he observed that the process requires "some sort" of preceding antigenic stimulus. (Tr. 212.) In that

[19] The authors also observed a significant increase of Th17 cells in patients with Sjogren's. (Holvast et al., *supra*, at Ex. V, p. 229.) Despite the increase in Th17 cells, the authors stress that the Sjogren's patients' overall disease activity did not change. (*Id.*) To explain this increase, Zhou et al. suggest that vaccines induce stable, long-term Th17 memory responses, and therefore these results are not pathogenic in Sjogren's. (*Id.*)

[20] Brauner et al. discuss another study showing that TLR7 was required for optimal antibody production post-immunization with the 2009 pandemic split vaccine in mice. (*Id.*) Those authors suggested that this was likely due to TLR7 recognition of viral RNA present in the split vaccine. (*Id.*)

regard, Dr. DeAngelo suggested that "the inclusion of an adjuvant may not be necessary for an unregulated autoinflammatory response in a susceptible host such as [petitioner]." (Ex. 42, p. 3.) He cites a literature review by Smatti et al., which found that "the literature supports the contention that viruses modify the clinical picture of autoimmune diseases," and suggests that "distinct antigen formulations may contribute to the varying rates of autoimmunity observed in different studies exploring the frequency of vaccine-associated autoimmunity."[21] (*Id.* (citing Smatti et al, *supra*, at Ex. 50).) Thus, in his reports Dr. DeAngelo cites a study by Chang et al. to opine that host-derived proteins can, in certain circumstances, have an adjuvant effect, and therefore, "the vaccine hemagglutinins, either alone or in combination with host proteins, is enough to induce an autoinflammatory state in a susceptible host." (*Id.* (citing Chang et al., *supra*, at Ex. 46); Tr. 230.)

During his testimony, Dr. DeAngelo testified that there are "two different ways" that hemagglutinins can induce autoinflammation, though he admitted "I'm not sure which way." (Tr. 230.) Dr. DeAngelo explained that "hemagglutinin is a foreign antigen" and "as we've seen following vaccination in this susceptible population in the Brauner article, you see this rise of inflammatory mediators and antibodies." (*Id.*) According to Dr. DeAngelo, "that means something's been recognized as bad. Whether that's the hemagglutinin or whether that's the hemagglutinin and a self-protein, I cannot say with any certainty." (*Id.* at 230-31.)

Chang et al. studied the mechanisms by which IgM coated ovalbumin-modified nanoparticles enhanced the immune response of mice to ovalbumin.[22] (Chang et al., *supra*, at Ex. 46.) Chang et al. observed enhanced T-cell activation and complement production by the particles after absorbing the proteins. (Chang et al., *supra*, at Ex. 46, pp. 127-28.) While this group coated the nanoparticles used in these experiments with murine IgM to enhance complement fixation and antigen responses, Dr. Wilfong stresses that these nanoparticles were also coated in recombinant ovalbumin, which is not a mouse-derived protein and is one of the most common adjuvants used in murine vaccination studies. (Ex. O, p. 2.) Moreover, Figure 2B demonstrates that the addition of murine IgM (host protein) to the ovalbumin nanoparticles fail to increase the immune response. (Chang et al., *supra*, at Ex. 46, p. 124.) Thus, Dr. Wilfong is persuasive in explaining that Chang et al. does not show a host protein acting as the adjuvant in this experiment.

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[21] Dr. Rose suggested the Smatti study makes a "strong case" that several infectious agents may lead to particular diseases. (Ex. P, p. 2.) However, Dr. Rose explained that "[t]he only well documented example of multiple autoimmune diseases associated with the same infection is Epstein-Barr virus infection," which has not been linked to UTCD. (*Id.*) Dr. Rose stressed that the Smatti study focused on living, infectious organisms. (*Id.*) The most cited example of a non-viable vaccine producing an autoimmune disease was during the 1970's swine flu epidemic when the flu vaccine was linked to an increased occurrence of GBS. However, Dr. Rose explained that these cases of GBS only lasted a few weeks, and "not at all like the chronic inflammatory disease" UCTD. (*Id.*)

[22] Dr. Rose explained that "[n]anoparticles are highly sensitive to size and surface, and [therefore] their use in vaccines is still speculative." (Ex. P, p. 3.)

3. Epidemiological Evidence and the ASIA Concept

Even in the absence of an identified autoantibody, or evidence of polyclonal B cell activation, an epidemiological association between undifferentiated connective tissue disease and the flu vaccine could still potentially support a causal theory. In that regard Dr. DeAngelo cites to ASIA as an identification of a relevant category of vaccine-triggered immune-mediated diseases even if it does not provide mechanistic evidence of causation. Here, however, the epidemiological evidence filed in this case fails to demonstrate a causal link between the flu vaccine and the onset or aggravation of UCTD.

As a general matter, it is true that petitioners in the Vaccine Program are not required to present epidemiological evidence to establish their causation burden under *Althen*. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325 (Fed. Cir. 2010). However, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole*, 726 F. App'x at 811 (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, *where such evidence is submitted*, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.") (emphasis added)); *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148-49 (Fed. Cir. 1992) (considering negative epidemiological studies).

Respondent cites a number of studies demonstrating the safety of the flu vaccine and the lack of a causal link with onset or aggravation of UCTD. A study conducted by Saad et al. (2011), evaluated 1668 patients with autoimmune rheumatic disease, including 69 with MCTD, which found no major relapses triggered by influenza vaccination. (Saad et al., *supra*, at Ex. A, Tab 10.) The study's main hypothesis was to evaluate the safety of the flu vaccine in connective tissue disease patients, while the safety and disease stability was investigated secondarily. (*Id.*) The SLE disease index, a calculation used to gauge disease activity, did not increase after vaccination in the study. (*Id.* at 1071.) This strongly suggests that the flu vaccine had no impact on the subjects' disease course, and furthermore, that the vaccine does not lead to connective tissue disease flares.

A review by the European League Against Rheumatism (2011) concluded that flu vaccination did not cause SLE flares, systemic sclerosis, or granulomatosis with polyangiitis, ultimately recommending inactivated flu vaccinations to rheumatic disease patients. (van Assen, *supra*, at Ex. A, Tab 12.) Dr. Wilfong relies on these studies to opine that "there is substantial evidence that influenza vaccinations are safe and do not exacerbate systemic rheumatologic conditions." (Ex. A, p. 6.) Another review, Liao et al. (2016), combined data from clinical trials, including 13 studies with data on FELDAI scores, for a total of 1,106 patients, including low, moderate and stable disease courses. (Liao et al., *supra*, at Ex. C, Tab 14, p. 5.) Trivalent, bivalent, and univalent influenza vaccines were used in the studies. (*Id.*) The authors concluded that "[t]here was [a] lack of direct evidence[] to verify that influenza can trigger exacerbation and

induce serious events." (*Id.* at 11.) Some patients with serious adverse events had other baseline diseases. (*Id.*) Liao et al. highlight the fact that influenza vaccines produce immunological responses during the first few weeks following vaccination. (*Id.*) If the vaccination triggered disease exacerbation, the authors stress that "it would be expected to happen particularly during this early period." (*Id.*) Yet, in their review, the duration between vaccination and occurrence of adverse events was greater than four weeks in some reported cases. (*Id.*)

Subsequently, van Assen et al. (2011) conducted a review of the reports that formed the basis for the EULAR review. (S. van Assen et al., *Vaccination in Adult Patients with Auto-Immune Rheumatic Diseases*, 10 AUTOIMMUNITY REVIEWS 341 (2011) (Ex. A, Tab 11).) The authors questioned whether vaccines cause significant harm to patients with autoimmune inflammatory rheumatic disease, generally, and specifically, in those with unstable disease and those using immunomodulating agents. (*Id.* at 345.) Upon their review, van Assen et al., reported no increase in disease activity among rheumatoid arthritis and lupus patients following influenza vaccination. (*Id.*) Other studies in lupus patients found either no flare or mild flares (up to 35%). (*Id.*) However, the authors caution that these studies did not include disease-controls, making their interpretation difficult. (*Id.*) Likewise, no flares were reported in Wegener granulomatosis or systemic sclerosis patients post influenza vaccination. (*Id.*) Of note, in all of the aforementioned studies the authors note that inactivated influenza vaccines were used. The authors furthermore acknowledge that many case series and case reports regarding the side effects of vaccination in autoimmune inflammatory rheumatic disease have been published, though they were excluded from this review since the "these cannot distinguish natural course of the underlying AIIRD from possible adverse effects caused by vaccination." (*Id.*)

Lastly, Puges et al. (2016), presented a literature review on the immunogenicity of influenza and pneumococcal vaccines in systemic lupus erythematosus. (Puges et al., *supra*, at Ex. J.) The influenza study contained three studies with a combined 1,598 patients and 800 controls that integrated SLEDAI scoring. (*Id*. at 1666.) Patients received an inactivated trivalent vaccine containing three viral strains, AH1N1, AH3N2 and B. (*Id.* at 1665.) In this study 594 patients were systematically scored. (*Id.* at 1670, Fig. 6.) The results from this study revealed that the change in SLEDAI score pre-and-post influenza vaccination was 0.6, not reaching statistical significance. (*Id.*) According to Dr. Wilfong, the change in SLEDAI score associated with any increased treatment for lupus is 1.5. (Tr. 297-98.) "And so there's no evidence for this very large meta-analysis that influenza vaccination was associated with increased disease activity in lupus." (*Id.* at 298.)

Addressing these studies, Dr. DeAngelo notes that they primarily center around the recommendation from large committees, such as the EULAR's conclusion that vaccination did not cause disease flares in SLE, systemic sclerosis, or granulomatosis with polyangiitis. (Ex. 23, p. 9 (citing van Assen et al., *supra*, at Ex. A, Tab 12).) He explains that such conclusions assume that all connective tissue diseases and patients are the same, and that, in the case of the 2011 EULAR article, the authors noted that "[m]ore research is needed, particularly regarding the incidence of vaccine-preventable

infectious diseases and the safety of vaccination in patients," with autoimmune inflammatory rheumatic diseases ("AIIRD"). (*Id.* (quoting van Assen et al., *supra*, at Ex. A, Tab 12).) Dr. DeAngelo criticizes respondent's reliance on van Assen and Puges et al. in particular because they assume that "all connective tissue diseases and patients are the same." (*Id.*) During the hearing, however, Dr. DeAngelo suggested that the results of the Brauner et al. study would be the same in patients with undifferentiated tissue disease, despite the fact that Brauner et al.'s study involved patients with Sjogren's syndrome. (Tr. 190.) According to Dr. DeAngelo, some connective tissue diseases are "tightly linked." (*Id.*) On direct examination, petitioner's counsel inquired:

> Q: . . . Do you believe the outcome of [Brauner et al.] would have been any different with the connective tissue disease being the subject disease as opposed to --
>
> A: None of the ones that I believe are tightly linked -- that would be your lupus, [MCTD], [UCTD], dermatomyositis, polymyositis, that group -- lupus, scleroderma, CREST, that group, I think the results would be the same. Would it be the same with ankylosing spondylitis, psoriatic arthritis, and Reiter's syndrome? Probably not, but, you known, I mean, who knows?

(*Id.*)

The literature filed in this case indicates that the essence of undifferentiated connective tissue disease is "the existence of conditions characterized by the presence of clinical and serological manifestations suggestive of autoimmune diseases but not sufficient to make a diagnosis of a defined CTD." (M. Mosca et al., *Undifferentiated Connective Tissue Diseases (UCTD)*, 6 AUTOIMMUNITY REVIEWS 1, 1 (2006) (Ex. 65).) To that end, there is obvious overlap between the clinical manifestation of undifferentiated tissue disease and other connective tissue diseases, an overlap that Dr. DeAngelo himself endorses. Dr. DeAngelo cannot use the distinction between these related conditions as both a sword and a shield. If Dr. DeAngelo's preferred Brauner study is relevant despite examining Sjogren's symptoms, then the epidemiology cited by respondent's experts is also relevant. Conversely, if the broader epidemiology is distinguishable, then Dr. DeAngelo's reliance on Brauner et al. is similarly suspect.[23] Considering all of this, the epidemiologic evidence when considered as a whole preponderates against a finding that the flu vaccine can cause or aggravate undifferentiated connective tissue disease.

To the extent petitioner urges that ASIA literature counsels otherwise as a matter of epidemiology, I have reviewed this literature and do not find that it bolsters petitioner's theory of causation. Dr. Levinson's critique of the concept is well taken. I have also previously addressed the merits of ASIA based on reports and testimony of its originator and concluded that it is not sound and reliable as a theory of causation under *Althen* prong one. *J.F. v. Sec'y of Health & Human Servs.*, No. 13-799V (Fed. Cl.

[23] Notable in that regard Dr. Wilfong opines that B cell dysregulation is thought to be a hallmark of Sjorgren's syndrome more so than other connective tissue diseases. (Tr. 316.)

Spec. Mstr. Sept. 9, 2022). Other special masters have also been critical of the concept. *E.g.*, *Decker v. Sec'y of Health & Human Servs.*, No. 15-71V, 2020 WL 7889059, at *32 (Fed. Cl. Spec. Mstr. Dec. 14, 2020); *Phillips v. Sec'y of Health & Human Servs.*, No. 16-906V, 2020 WL 7767511, at *21 (Fed. Cl. Spec. Mstr. Nov. 23, 2020); *Salerno v. Sec'y of Health & Human Servs.*, No. 16-1280V, 2020 WL 3444163, at *11 (Fed. Cl. Spec. Mstr. May 29, 2020); *Pearson v. Sec'y of Health & Human Servs.*, No. 16-9V, 2019 WL 3852633, at *13 (Fed. Cl. Spec. Mstr. Jul. 31, 2019); *Suliman v. Sec'y of Health & Human Servs.*, No. 13-993V, 2018 WL 6803697, at *27 (Fed. Cl. Spec. Mstr. Nov. 27, 2018) ("No special masters have ever found ASIA or ASIA-like theories to be persuasive"). Despite earlier reports filed in this case, petitioner clarifies that she is "not advocating . . . ASIA as the mechanistic explanation for Petitioner's onset and/or aggravation of her asymptomatic/subclinical UCTD." (ECF No. 97, p. 13.)

c. Significant Aggravation (*Loving* prongs one through three)

Assuming *arguendo* that petitioner did prove a medical theory demonstrating that her flu vaccination could have caused or aggravated her UCTD, the remainder of the *Loving* test queries whether petitioner would be able to show that it did do so in this particular case. The threshold question in that remaining analysis is whether petitioner's condition was, in fact, significantly aggravated. To demonstrate significant aggravation, the Vaccine Act requires a "change for the worse in a preexisting condition," and "markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4). Under the *Loving* test, petitioner demonstrates this by showing (1) her condition before the vaccination, (2) her current condition, and (3) that her current condition constitutes a significant aggravation of her prior condition. There are two cases, *Locane* and *Sharpe,* that illustrate the Federal Circuit's significant aggravation analysis with regard to the evolution of a petitioner's clinical course. *Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375 (Fed. Cir. 2012); *Sharpe v. Sec'y of Health & Human Servs.*, 964 F.3d 1072 (Fed. Cir. 2020).

In *Locane*, petitioner alleged her Crohn's disease, an inflammatory bowel disease, was significantly aggravated by the Hepatitis B vaccine. *Locane*, 685 F.3d at 1377-78. The special master determined that petitioner failed to preponderantly prove her significant aggravation claim "because the course of her disease was not affected by the vaccination." *Id.* at 1378. The Federal Circuit affirmed, explaining that the special master considered "the relevant evidence of record, [drew] plausible inferences and articulated a rational basis for the decision." *Id.* at 1381-82. The Court further indicated that petitioner was "given ample opportunity to develop her significant aggravation claim but 'failed to present persuasive evidence that separates [her] problems from an expected course of Crohn's disease.'" *Id.* at 1382.

In *Sharpe,* petitioner alleged L.M. had a preexisting "seizure disorder" and the administration of the several childhood vaccines at her six-month wellness check-up significantly aggravated L.M.'s pre-existing condition. *Sharpe*, 964 F.3d at 1076-77. The special master denied petitioner's significant aggravation claim because L.M.'s genetic mutation, and not the vaccination, was the sole, substantial cause of L.M.'s seizure disorder. *Id.* at 1080. The Circuit found the special master's analysis "required

[p]etitioner to prove the expected outcome for a child with a DYNC1H1 gene mutation and to show that L.M.'s current, post-vaccination condition was worse than that expected outcome." *Id.* at 1081. The Circuit stated, "a court should consider all evidence in the record, including evidence of other possible sources of injury. There is, however, a fine line between a court properly considering evidence in the record . . . and improperly placing the burden on the petitioner to prove that her significantly aggravated condition was not caused by her gene mutation." *Id.* at 1082. The Court distinguished the special master's decision from *Locane* stating, in *Locane* "the special master did not require the petitioner to prove that her significantly aggravated condition was not caused by her preexisting condition. Instead, the special master found that the petitioner's condition 'was not affected by the vaccination.'" *Id.*

In this case, petitioner contends that prior to her influenza vaccination she demonstrated no objective signs or symptoms of active connective tissue disease. (ECF No. 97, p. 16 (citing Ex. 10, p. 34; Ex. 3, p. 7).) Petitioner contends that in the two-week window following administration of her influenza vaccine, she experienced a "clinically symptomatic event," demonstrated by bilateral shoulder/arm arthralgia/myalgia, which progressed and worsened over the weeks/months that followed to include rash, Raynaud's syndrome, swollen hands and PIP joints, forearm/knee pain, synovitis, hair loss, and facial paresthesia—eventually leading to a diagnosis of UCTD. (ECF No. 97, p. 16 (citing Ex. 12, pp. 5-6, 19; Ex. 10, pp. 5, 11, 14); *see also* Tr. 66-78; 119-149.)

Respondent's experts did not dispute the overall decline in petitioner's post-vaccination health. (Tr. 323-24; 384-86.) Rather, respondent's experts suggested that petitioner's increase in symptoms post-vaccination was the natural and expected disease course—in which her vaccination played no significant role. (*Id.* at 284-86.) Dr. Wilfong opined that petitioner began exhibiting symptoms of an emerging connective tissue disease in the summer of 2013. (*Id.* at 266.) Dr. Wilfong testified that petitioner's providers became worried about an emerging CTD in June of 2013, when an ANA and sudden CRP were observed. (*Id.* at 268.) By August 2013 petitioner reported morning stiffness. (*Id.*) Dr. Wilfong explains that morning stiffness is a diagnostic symptom for inflammatory arthritis—when overnight as patients are not using their joints, "their joints get stiffer, and in the morning, they're stiff for an hour or two, and the more they use their joints, the better they do." (*Id.*) The fact that morning stiffness was noted in Dr. Crane's notes, according to Dr. Wilfong, "is concerning that the [CTD] was definitely emerging by August 2013." (*Id.* at 269.) At the same time, petitioner's RNP was found to be exceptionally high titer. (*Id.*) Dr. Wilfong explains that this is the "pathognomonic antibody for . . . mixed connective tissue disease, and so that's expected, given [petitioner's] ultimate clinical course, but, again, it's very concerning that we are really hearing the first true clinical obvious manifestation of her MCTD." (*Id.*)

Dr. Wilfong testified that she relies upon two studies, one on rheumatoid arthritis and another on systematic lupus erythematous, to describe the presence of the preclinical phase. (Tr. at 277 (citing Deane & El-Gabalawy, *supra*, Ex. A, Tab 3; Melissa Arbuckle et al., *Development of Autoantibodies Before the Clinical Onset of*

Systemic Lupus Erythematosus, 349 N. ENGL. J. MED. 1526 (2003) (Ex. A, Tab 1)).) Based on these studies, Dr. Wilfong observes that the interval time from the positive RNP test to the onset of symptoms, was .2 years, or approximately two-and-a-half months, "which is very close actually to the Petitioner's course." (*Id.* at 278.) The studies suggest that "the antibodies accumulate, and then there's a tipping point," though Dr. Wilfong explains that "we don't really understand what causes that tipping point . . . what causes somebody to transform from true preclinical with antibodies but no symptoms to starting to get their symptoms and they're more characteristic symptoms." (*Id.* at 278-79.)

Ultimately, Dr. Wilfong disagreed with petitioner's testimony that she developed all of her CTD symptoms post-vaccination. (Tr. 285.) Dr. Wilfong stresses that "she already had the antibodies. She already had arthralgia. She had morning stiffness noted. She had leukopenia prior to vaccination. Were these enough that I would have said to her in the office, You definitely have a connective tissue disease? No." (*Id.*) However, she stresses that petitioner's presentation was suggestive of an emerging CTD prior to vaccination. (*Id.*) Based on her clinical experience, she stresses that "[t]his is what patients do . . . they start with some vague complaints and then start accumulating one symptom after another over time." (*Id.* at 285-86.) Dr. Wilfong opines that petitioner showcased a "relatively typical progression" of CTD. (*Id.*)

In contrast, Dr. Rushing agreed petitioner had preexisting UCTD (Tr. 64-66), but opined that it was entirely asymptomatic prior to vaccination and significantly worsened following her influenza vaccination on November 8, 2013. (Tr. 77.) Specifically, he observed that petitioner developed pain in her shoulders and arms, and subsequently developed Raynaud's. (*Id.*) Furthermore, she developed swelling in her hands and fingers, she had hair loss, and ultimately developed trigeminal neuropathy—"a whole new set of symptoms which she didn't have before the vaccine." (*Id.*) However, I asked Dr. Rushing, "Apart from the fact of her having had a flu vaccine, is there anything unusual about Ms. Volpe's transition from subclinical to clinical connective tissue disorder or disease?" (Tr. 101.) Consistent with Dr. Wilfong's opinion that petitioner followed a "relatively typical progression," Dr. Rushing initially answered that no, he is not aware of anything unusual in petitioner's transition from subclinical to clinical disease.[24] (*Id*.) I also asked Dr. Rushing whether the standard of care for CTD includes screening for environmental triggers and, if so, how often in Dr. Rushing's experience an environmental trigger is identified. (*Id*.) He testified that a complete evaluation and history is part of the standard of care, but that "[l]ots of times you cannot determine [the trigger]." (*Id.* at 102.) He testified that the medical literature on mixed and undifferentiated connective tissue diseases suggests that "as high as 25 percent [of

[24] On redirect, however, petitioner's counsel re-asked essentially the same question, but offering the specific prompt "do you deem it unusual for someone to be subclinical as you deemed Ms. Volpe to be and then to present with the degree of symptomology that she did in such a short period of time?" (Tr. 104.) At that point, Dr. Rushing offered the opinion that the rapidity of petitioner's transition to overt UCTD was unusual. (*Id.* at 104-05.) Respondent objected to petitioner's counsel's leading of the witness. (*Id.* at 105.) Dr. Rushing did not attempt to reconcile his testimony on redirect examination with this prior testimony.

cases] you can't identify a trigger." (*Id*.) Dr. Rushing suggested that among that 25 percent, an environmental trigger is "probably undiscovered," rather than absent, but could not give "an absolute answer on that." (*Id*.)

In light of the above, I do not find preponderant evidence on this record that petitioner's vaccination significantly aggravated her condition. On the whole, Dr. Wilfong is more persuasive in explaining that petitioner had overt signs of an emerging connective tissue disease prior to the vaccination at issue and followed a "typical progression" of the condition. Dr. Rushing likewise agreed that the general progression of petitioner's condition was not unusual, but to the extent he opined it was unusually rapid post-vaccination, this was based on his assumption that petitioner was asymptomatic pre-vaccination. I have not required petitioner to prove that her post-vaccination condition was worse than the expected outcome. Instead, I find that the evidence taken as a whole shows that the course of her UCTD was not likely to have been affected by the vaccination. This finding is consistent with *Locane*. It is also further reinforced by the discussion of the treating physician opinions below.

d. Logical sequence of cause and effect showing the vaccination was the cause or aggravation of petitioner's injury (*Althen* Prong Two / *Loving* Prong Five)

The second *Althen* prong / fifth *Loving* prong requires proof of a logical sequence of cause and effect showing that the vaccine was the reason for the injury, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006); *Grant*, 956 F.2d at 1148. However, medical records and/or statements of a treating physician do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* 42 U.S.C. §300aa-13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) (stating that "there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Here, I find that there is not preponderant evidence that petitioner's treating physicians concluded that her flu vaccination caused or significantly aggravated of her preexisting UCTD.

The medical record closest to supporting petitioner's contention is Dr. Ramsey-Goldman's note from April 15, 2014. (Ex. 12, p. 23.) Dr. Ramsey-Goldman noted petitioner "[g]ot a flu shot in 11/2013, ten days later developed myalgias in shoulders and upper arms." (*Id.*) However, Dr. Ramsey-Goldman did not ultimately opine as to the cause of petitioner's symptoms. Dr. Ramsey-Goldman also explained that petitioner underwent a repeat MRI on her neck and shoulder after her symptoms started, and was told she had an osteophyte on C5, though she was "unsure if [it] was causing symptoms." (*Id.*) In context, Dr. Ramsey-Goldman's discussion of petitioner's MRI findings more strongly suggests her consideration of a mechanical cause for petitioner's

shoulder pain. Similarly, on May 14, 2014, petitioner presented to Dr. Broderick, who also noted "patient states that 10 days after, she received a flu shot. She started experiencing bilateral shoulder and bilateral arm pain." (Ex. 14, p. 2.) Dr. Broderick concluded that petitioner's cervical spine MRI showing a bulging disc are not a major contributing factor to her right shoulder and right wrist symptoms although "an EMG of the bilateral upper extremities [could] distinguish between a neurological versus rheumatological problem." (*Id.* at 4.) Dr. Broderick made no other mention of petitioner's vaccination. (*See id.* at 2-4.)

Upon my review of petitioner's medical records, no other physicians attributed or contemplated vaccine causation for petitioner's UCTD. While treating physician records are given significant weight, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012); *see also Devonshire v. Sec'y of Health & Human Servs.*, No. 99-031V, 2006 WL 2970418, at *19 (Fed. Cl. Spec. Mstr. Sept. 28, 2006) (medical expert's "*post hoc ergo prompter hoc* reasoning . . . has been consistently rejected by the Court and is 'regarded as neither good logic nor good law'") (quoting *Fricano v. U.S.*, 22 Cl. Ct. 796, 800 (1991) (emphasis in original)).

In support of a logical sequence of cause and effect, petitioner stresses that her treating rheumatologists agreed that she demonstrated no objective signs or symptoms of active connective tissue disease prior to vaccination, and thus did not recommend any therapy or treatment. (ECF No. 97, p. 16 (citing Ex 10, p. 34 ("no signs or symptoms" of MCTD); Ex. 3, p. 7 ("positive ANA could be related to the recent diagnosis of autoimmune thyroid diseases")).) As discussed above, petitioner contends that she suffered a "clinically symptomatic event" of newly developed bilateral shoulder / arm arthralgia / myalgia, which progressed over the following weeks and months, leading to the diagnosis of UCTD and immunosuppressant therapy program. (Ex. 12, pp. 5-6, 19; Ex. 10, pp. 5, 11, 14). The records cited by petitioner in support of *Althen* prong two / *Loving* prong five document petitioner's worsening undifferentiated connective tissue disease. (Ex. 12, pp. 5-6 (noting petitioner "was asymptomatic"); *id.* at 22 ("agree[ing] with the assessment of suspected CTD with minimal sxs"); Ex. 10, p. 5 (assessing facial paresthesia, intermittent leukopenia, intermittent knee pain); *id.* at 11 (same); *id.* at 14 (noting mild hair loss).) However, none of these records suggest that petitioner's symptoms were caused or significantly aggravated by her flu vaccination.

Lastly, petitioner contends that "[t]here is no evidence or recent illness, infection, and/or other environmental factor to otherwise explain this sudden and dramatic onset of symptomatic connective tissue disease." (ECF No. 97, p. 16.) In this Program, however, absence of another cause is not persuasive evidence in support of petitioner's burden to show causation. *See D.G.*, 2019 WL 2511769, at *183 ("[T]he Federal Circuit in *Grant* state[]d [that] petitioner's burden is to prove vaccine causation with affirmative evidence. Saying since there is no other cause, it has to be the vaccine is not affirmative proof.") (citing *Grant,* 956 F.2d at 1149).

To the extent petitioner could otherwise support an *Althen* prong two / *Loving* prong five showing based on expert opinion, the same issues that render petitioner's experts less persuasive with respect to *Loving* prongs one through four likewise prevent them from effectively opining with respect to any logical sequence of cause and effect to suggest her vaccine caused or aggravated her condition.

e. Proximate temporal relationship between vaccination and injury (*Althen* prong three / *Loving* prong six)

The third *Althen* prong / sixth *Loving* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury. *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Petitioner alleges that she meets the medically acceptable temporal relationship between flu vaccination and significant aggravation. (ECF No. 97, p. 16.) Dr. DeAngelo relies on the Brauner study, which evidenced an increase in IgG response and polyclonal activation of B cells occurred within 1-3 weeks after vaccination. (*Id.* (citing Ex. 62, p. 4; Brauner et al., *supra*, at Ex. 63, p. 3).) Petitioner contends that her symptomatic rheumatic disease first manifested approximately two weeks following administration of her influenza vaccine. (ECF No. 97, p. 17 (citing Ex. 2, pp. 7-9; Ex. 12, pp. 23, 26-29; Ex. 64, p. 1).) Therefore, petitioner alleges that her onset of rheumatic disease expression is consistent with the timeframe espoused in Brauner for an anticipated / expected rise in antibody response and polyclonal activation of B cells following vaccination. (ECF No. 97, p. 17.) However, I have concluded that the results of Brauner et al. are not broadly applicable to petitioner's case, for reasons enumerated above. Without more, petitioner fails to preponderantly establish a proximate temporal relationship between her vaccination and her UCTD.

In any event, even if the onset of petitioner's post-vaccination symptoms could arguably be consistent with an immunologic injury broadly, demonstration of a temporal relationship alone is insufficient to prove causation. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. *See*, *e.g.*, *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

VI. Conclusion

Petitioner has my sympathy for the pain and suffering she endured and the symptoms she suffers from presently. However, for all the reasons discussed above, after weighing the evidence of record within the context of this program, I cannot find by preponderant evidence that the flu vaccine caused or significantly aggravated petitioner's undifferentiated connective tissue disease. Accordingly, this claim is **DISMISSED**.[25]

IT IS SO ORDERED.

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

[25] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.