In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-260V
Filed: December 20, 2018
To be Published

S.E.H.,	*	
	*	
Petitioner,	*	
	*	Influenza ("flu") vaccine; mixed
v.	*	connective tissue disease ("MCTD");
	*	failure to provide a persuasive
SECRETARY OF HEALTH	*	medical theory of causation
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	
	*	

Michael A. Firestone, San Mateo, CA, for petitioner.
Linda S. Renzi, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

On March 13, 2015, petitioner filed a petition pro se under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that influenza ("flu") vaccine administered in her left deltoid on September 20, 2012 caused her mixed connective tissue disease ("MCTD") whose onset was October 3, 2012 with joint pains. Pet. Preamble and ¶¶ 2, 4; Pet. Tab 2.

On August 11, 2015, petitioner retained counsel. On January 4, 2016, petitioner filed an amended petition, alleging in the alternative that her September 20, 2012 flu vaccination caused significant aggravation of an underlying autoimmune disease that was asymptomatic until early October 2012. Am. Pet. at ¶ 20.

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would constitute a clearly unwarranted invasion of privacy. **This means the decision will be available to anyone with access to the Internet.** When such a decision is filed, petitioner has 14 days to identify and move to redact such information prior to the document's enclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall redact such material from public access. Petitioner filed a motion to redact on December 27, 2018 which the undersigned granted on December 28, 2018.

A hearing was held on August 29, 2017. Testifying for petitioner were petitioner, petitioner's husband, and Dr. S. Sohail Ahmed. Testifying for respondent was Dr. Mehrdad Matloubian.

On April 27, 2018, petitioner filed her post-hearing brief.

On August 31, 2018, respondent filed his post-hearing brief.

On November 16, 2018, petitioner filed her reply to respondent's post-hearing brief.

Because the undersigned finds petitioner has failed to present a persuasive scientific or medical theory to associate causally her September 20, 2012 flu vaccination with MCTD or, in the alternative, to prove flu vaccine significantly aggravated her prior rheumatologic disease, the undersigned dismisses this case.

FACTS

Prevaccination Records

Petitioner was born on July 17, 1955.

On October 7, 1999, petitioner received flu vaccine[2] in her left deltoid. Med. recs. Ex. 16, at 1.

On February 8, 2000, petitioner saw Dr. Anjali Sagdeo, and gave a history that she received a flu vaccination in her left arm and, since then, had pain in her left arm and difficulty raising it.[3] Med. recs. Ex. 12, at 1 (same record filed as Ex. 69, at 1). She saw a worker's compensation doctor. On physical examination, petitioner had tenderness in her left upper arm

[2] In the 1999-2000 flu vaccine season, the trivalent flu vaccine contained A/Sydney/5/97-like virus (H_3N_2), A/Beijing/262/95-like virus (H_1N_1), and B/Beijing/184/93-like (Yamagata lineage) virus. Update: Influenza Activity – United States and Worldwide, 1998-99 Season, and Composition of the 1999-2000 Influenza Vaccine, 48 MORBIDITY AND MORTALITY WEEKLY REPORT (MMWR) 18:374-78 (May 14, 1999), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4818a2.htm.

[3] Petitioner's description of left arm pain and difficulty raising her left arm a day after vaccination may have been SIRVA (shoulder injury related to vaccine administration), which became a Table injury after March 21, 2017. National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table; Delay of Effective Date, 82 Fed. Reg. 34:11321 (Feb. 22, 2017). The Vaccine Injury Table is at 42 C.F.R. § 100.3(a). The Qualifications and aids to interpretation, § 100.3(c)(10), state "SIRVA manifests as shoulder pain and limited range of motion occurring after administration of a vaccine intended for intramuscular administration in the upper arm. The symptoms are thought to occur as a result of unintended injection of vaccine antigen or trauma from the needle into and around the underlying bursa of the shoulder resulting in an inflammatory reaction. SIRVA is caused by an injury to the musculoskeletal structures of the shoulders (e.g. tendons, ligaments, bursae, etc.)." One of the manifestations of SIRVA is "(iii) Pain and reduced range of motion … limited to the shoulder in which the intramuscular vaccine was administered…." Id. The Vaccine Injury Table requires onset of SIRVA within 48 hours of vaccination. Id. at (a). Petitioner's description of her left arm pain and difficulty raising her left arm a day after vaccination may have been SIRVA.

and decreased abduction. Dr. Sagdeo's diagnosis was tendinitis[4] – inflammation secondary to injury from an intramuscular injection. Petitioner was right-handed. Dr. Sagdeo suggested she follow up with the worker's compensation doctor. Id.

On February 29, 2000, petitioner saw Dr. Dinesh N. Bhuva, giving a history that she received flu vaccine in her left arm in November 1999 and, the next day, had a punched arm. She could not sleep on the shoulder or abduct her arm. She could not pull up her pants. Her range of motion declined. The doctor diagnosed petitioner with tendinitis. An examination for her left shoulder pain revealed tenderness at the supraspinatus[5] insertion. X-ray revealed calcification of the supraspinatus.[6] Med. recs. Ex. 69, at 2.

On March 9, 2000, petitioner saw Dr. Sagdeo, to rule out food and alcohol allergies. Petitioner states her face got red with [the following word was redacted]. This also happened with certain foods. Dr. Sagdeo referred petitioner to an allergist. He also diagnosed her with hypothyroidism.[7] Med. recs. Ex. 12, at 4 (same record filed as Ex. 69, at 4).

On March 29, 2000, petitioner saw Dr. Bhuva for a recheck of her left shoulder. Id. at 4. Petitioner's last injection helped a lot for three weeks, but now her left shoulder hurt again. It

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[4] Tendinitis is "inflammation of tendons and of tendon-muscle attachments. . . ." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1881 (32nd ed. 2012) [hereinafter "Dorland's"].

[5] Supraspinatus tendinitis or painful arc syndrome occurs in the shoulder. The shoulder joint owes its stability to the rotator cuff muscles—which are four small muscles located around the shoulder joint which help with movement, but importantly their tendons stabilize the head of the humerus within the joint capsule. The tendon of one of these muscles—the supraspinatus--commonly impinges on the acromion (the bone forming the tip of the shoulder) as it passes between the acromion and the humeral head. The supraspinatus muscles help abduct (lift up sideways) the arm. Any friction between the tendon and the acromion is normally reduced by the subacromial bursa—a fluid filled sac between the supraspinatus tendon and the acromion. Arthritis can cause painful arc syndrome. Supraspinatus tendinitis is very common and typically seen in people aged 25-60. It can also result from gradual degeneration with wear and tear or other inflammatory disorders, such as rheumatoid arthritis. An x-ray may show calcification. Chronic trauma and impingement may lead to osteoarthritis of the shoulder. Supraspinatus tendinitis (painful arc syndrome), MYVMCVIRTUALMEDICALCENTRE, https://www.myvmc.com/diseases/supraspinatus-tendinitis-painful-arc-syndrome/ (last visited November 26, 2018). The humerus is "the bone that extends from the shoulder to the elbow." Dorland's at 873. "The humeral head is the 'ball' part of the ball and socket" making up the shoulder. Anatomy of the shoulder (glenohumeral joint/scapulo-thoracic joint), MYVMCVIRTUALMEDICALCENTRE, https://www.myvmc.com/anatomy/anatomy-of-the-shoulder-glenohumeral-jointscapulo-thoracic-joint/ (last visited November 26, 2018). Painful arc syndrome is "shoulder pain occurring at a particular portion of the arc described when the arm is abducted from the side to the fully raised position, as in inflammation of the tendons of the supraspinatus muscle." Dorland's at 1842.

[6] "Supraspinatus tendon calcification is thought to be due to the deposition of calcium hydroxyapatite crystals inside the supraspinatus tendon near the greater tuberosity of the humerus insertion point, and the calcium deposits in the supraspinatus tendon may be due to fibrosis, necrosis, tendon degeneration, or systemic non-degenerative causes. [citation omitted]." David C. Riley et al., Emergency department diagnosis of supraspinatus tendon calcification and shoulder impingement syndrome using bedside ultrasonography, 5 CRIT ULTRASOUND J 1-4, at 2-3 (2013).

[7] Hypothyroidism is "a deficiency of thyroid activity, characterized by decrease in basal metabolic rate, fatigue, and lethargy. . . ." Dorland's at 907. The most common cause of hypothyroidism is Hashimoto's thyroiditis or autoimmune hypothyroidism, but Hashimoto's is not the sole cause of hypothyroidism. Eren Berber, MD, Causes of Hypothyroidism. Hashimoto's thyroiditis is the most common cause, ENDOCRINEWEB, https://www.endocrineweb.com/conditions/hypothyroidism/causes-hypothyroidism (last visited November 2, 2018).

hurt with overhead reaching. Id.

On April 4, 2000, petitioner filled out an Allergy Questionnaire for Dr. Clayton A. Feldman. Med. recs. Ex. 12, at 1 (same record filed as Ex. 69, at 6). She said she had seasonal hay fever, food allergy, and drug allergy. She complained of nasal congestion, itchy eyes, swollen eyelids, dark circles under her eyes, and a sinus headache. Med. recs. Ex. 12, at 1. She said 20 years previously, she broke out in hives after receiving sulfa. Id. at 8. She told Dr. Feldman that she had years of sinus problems. Id. at 15. She had been getting erythema[8] of the face, nausea, and headaches in the past year. Id. at 16. Dr. Feldman's impression was that petitioner did not have a conventional food allergy, but food intolerances without food allergy. Id. Her symptoms sounded like a vascular reaction, such as migraine,[9] and he recommended she eliminate foods for which she had no tolerance. Id. at 12-13 (same record filed as Ex. 69, at 16-17).

On April 7, 2000, Dr. Feldman wrote a consultation report. Med. recs. Ex. 9, at 11. Petitioner said she had several years of minor sinus and seasonal allergy symptoms. In the past year, she had some concern about food allergy. She had been getting erythema of her face, nausea, and headaches from almost any kind of alcoholic beverage. She experimented with red and white wines, gin and tonic, and beer, and got reactions approximately 20 minutes after each. She had a similar reaction after a mushroom omelet one month ago, but this occurred only once. A few weeks earlier, she went on the Atkins diet for weight control, and since then her sinus headaches disappeared. She ate meat, fish, and limited carbohydrates, and took supplements, but no fruits, bread, pasta or sugars. She had a history of sulfa sensitivity. She had good relief from mild seasonal hay fever with antihistamines, Sudafed,[10] and topical steroids. Her physical examination was unremarkable except for slightly thickened red nasal membranes. The RAST[11] allergy testing was negative for fruits that she eliminated from her diet, including banana, lemon apple, orange, peach, strawberry, and melon. Dr. Feldman's impression was food intolerance without food allergy, and minimal seasonal and perennial allergic rhinitis. Id. Dr. Feldman stated petitioner really did not have a conventional food allergy. Her symptoms sounded like a vascular reaction, something like a migraine. Id. at 11, 13.

On May 3, 2000, petitioner went to Dr. Bhuva for a recheck of her left shoulder. Med. recs. Ex. 12, at 14 (same record filed as Ex. 69, at 18). She still had pain and could not do her hair. Id.

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[8] Erythema is "redness of the skin produced by congestion of the capillaries." Dorland's at 643.

[9] Migraine is "an often familial symptom complex of periodic attacks of vascular headache, usually temporal and unilateral in onset, commonly associated with irritability, nausea, vomiting, constipation or diarrhea, and often photophobia. Attacks are preceded by constriction of the cranial arteries, often with resultant prodromal sensory (especially ocular) symptoms and the spreading depression of Leão; the migraines themselves commence with the vasodilation that follows." Dorland's at 1166.

[10] Sudafed is "trademark for preparations containing pseudoephedrine hydrochloride." Dorland's at 1796. It is used as a nasal decongestant. Id. at 1542.

[11] RAST is an acronym for "radioallergosorbent test." Dorland's at 1593.

On May 15, 2000, petitioner's TSH[12] of 6.16 was consistent with hypothyroidism. Med. recs. Ex. 9, at 5.

On May 30, 2000, petitioner had an MRI to rule out rotator cuff tear as the cause of her left shoulder pain. Id. at 9.

On June 2, 2000, petitioner saw Dr. Michael W. Su for migraine headaches. Med. recs. Ex. 12, at 18. She had migraines triggered by certain foods: smoked foods and almonds. She thought she had some nausea with photophobia. She also had a urinary tract infection. Id.

On October 31, 2000, petitioner saw Dr. Gary Lee to have her thyroid checked. Med. recs. Ex. 16, at 24. She told Dr. Lee she felt exhausted over the prior week. Dr. Lee diagnosed petitioner with hypothyroidism. Id.

On January 24, 2001, petitioner saw Dr. Joel S. Saal for an orthopedic consultation. Med. recs. Ex. 11, at 1. Petitioner complained of low back pain and right leg hypesthesia.[13] The onset was December 15, 2000 while she was working as a nurse. She was using a slideboard to help a patient transfer when the patient's foot caught on the edge of the board and she reached over to pull it up and support the foot. She went to Urgent Care and received a Demerol[14] injection, Vicodin,[15] and Flexeril.[16] She was prescribed physical therapy twice a week and placed on work restrictions of no bending, twisting, or lifting. She described no improvement and each day when she would work, her pain became worse and was not relieved until she lay down at night. She stopped working for a number of days and her symptoms improved somewhat but still persisted and increased with any bending, lifting, or sitting for prolonged periods of time. Petitioner was taking Flexeril and Naprosyn.[17] Id. Dr. Saal diagnosed petitioner with probable annulus[18] tear, L4-L5 vs. L5-S1. Id. at 2. He suggested she supplant the anti-inflammatory medicine with exercises. Id.

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[12] TSH stands for "thyroid-stimulating hormone." Dorland's at 1902.

[13] Hypesthesia or hypoesthesia is "a dysesthesia consisting of abnormally decreased sensitivity, particularly to touch." Dorland's at 901.

[14] Demerol is "trademark for preparations of meperidine hydrochloride." Dorland's at 485. Meperidine hydrochloride is "a synthetic opioid analgesic, used as an analgesic to relieve moderate to severe pain. . . ." Id. at 1136.

[15] Vicodin is "trademark for combination preparations of hydrocodone bitartrate and acetaminophen." Dorland's at 2055. Hydrocodone is "a semisynthetic opioid analgesic derived from codeine but having more powerful sedative and analgesic effects." Id. at 878.

[16] Flexeril is "trademark for a preparation of cyclobenzaprine hydrochloride." Dorland's at 717. Cyclobenzaprine hydrochloride is "a compound structurally related to the tricyclic antidepressants, used as a skeletal muscle relaxant for relief of painful muscle spasms. . . ." Id. at 455.

[17] Naprosyn is "trademark for preparations of naproxen." Dorland's at 1232. Naproxen is "a nonsteroidal anti-inflammatory drug that is a propionic acid derivative, used in the treatment of pain, inflammation, osteoarthritis, rheumatoid arthritis, gout, calcium pyrophosphate deposition disease, fever, and dysmenorrhea and in the prophylaxis and suppression of vascular headache. . . ." Id.

[18] Annulus is "a ring or ringlike structure. . . ." Dorland's at 94.

On April 3, 2001, Dr. Saal performed a lumbar transforaminal[19] selective epidural block, in the left L5 position. Id. at 5.

On April 23, 2001, petitioner returned to Dr. Saal. Id. at 7. She had marked relief for a short period of time following the epidural injection, but no significant change in her symptoms. Her MRI showed only minor degenerative changes at L4-L5 with a slight annular bulge, but no evidence of significant abnormality. Dr. Saal's impression was probable discogenic pain, most likely from the L4-L5 segment. Id. He suggested petitioner change where she received physical therapy or, if that were unsuccessful, have a repeat epidural injection. In addition, he wanted petitioner to start acupuncture. Id.

On July 26, 2001, petitioner saw Dr. Su, complaining of coughing for one month. Med. recs. Ex. 16, at 26.

On September 21, 2001, Dr. Saal performed a lumbar intradiscal electrothermal annuloplasty ("IDET") on petitioner. Med. recs. Ex. 11, at 17.

On September 25, 2001, petitioner saw Dr. Harley B. Negin, complaining of headache, and palpitations for months. Med. recs. Ex. 69, at 29.

On October 18, 2001, Dr. Saal reevaluated petitioner. Med. recs. Ex. 11, at 20. She had no further leg pain after her IDET, but her back pain was the same. Id.

On November 29, 2001, Dr. Saal reevaluated petitioner. Id. at 21. She said she felt about 30 percent better. She had difficulty with long standing. Dr. Saal recommended a pool program. Id. She was to remain on temporary total disability through January 30, 2002. Id.

On January 3, 2002, Dr. Saal reevaluated petitioner. Id. at 22. She was markedly improved but still significantly symptomatic and limited. Her abdominal muscles were extremely weak. Dr. Saal recommended progression in her physical rehabilitation program. She was to remain on temporary total disability through March 30, 2002. Id.

On January 29, 2002, petitioner saw Dr. Su, complaining of problems with her back. Med. recs. Ex. 69, at 30. She was continuing to undergo therapy for her back. Id.

On February 28, 2002, Dr. Saal reevaluated petitioner. Med. recs. Ex. 11, at 24. She was improving somewhat from her flare up. The symptoms were unchanged, mostly in her back. She took Prednisone[20] and then went on Vioxx. Her physical examination showed painful lumbar flexion and extension. Dr. Saal prescribed acupuncture and extended her total temporary disability through April 20, 2002. Id.

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[19] Transforaminal is "through or across a foramen." Dorland's at 1952. Foramen is "a natural opening or passage, especially one into or through a bone." Id. at 729.

[20] Prednisone is "a synthetic glucocorticoid derived from cortisone, administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders." Dorland's at 1509.

On April 24, 2002, Dr. Saal reevaluated petitioner. Id. at 25. She described persistent symptoms: pressure in her low back and some symptoms in her right leg. Overall, she described herself as 50-60 percent improved. Dr. Saal injected Marcaine[21] and Decadron[22] into the soft tissue region in the right L5-S1 interspace because it was tender. Id. This decreased petitioner's leg pain but had no effect on the pressure sensation in her low back. Id.

On June 27, 2002, Dr. Saal reevaluated petitioner. Id. at 26. Petitioner said she was progressively improving. She had daily symptoms, but could tolerate them. Id. She remained on total temporary disability through August 30, 2002. Id.

On July 11, 2002, Dr. Saal gave petitioner soft tissue injections with Marcaine, Depo-Medrol,[23] and Decadron after she complained about a slight increase in symptoms when she reduced her dosage of Vioxx. Id. at 27, 28. Her disability status remained unchanged. Id. at 27.

On August 20, 2002, Dr. Saal reevaluated petitioner. She said she did not get a good response from the intramuscular and deep paraspinal soft tissue injections, and did not receive lasting relief from corticosteroids. Id. at 29. Her symptoms were now back to her baseline. She tolerated the increased level of exercise from three months ago. Dr. Saal hoped to increase her exercise tolerance and if that did not succeed, move toward a lumbar epidural. Id.

On October 15, 2002, Dr. Saal reevaluated petitioner. Id.at 30. Petitioner said she had a little flare up of ankle pain and secondarily back pain, worse on the right than on the left. It occurred while she was exercising more aggressively using the treadmill and doing squatting exercises. It was similar to what she experienced at the early onset of her low back pain syndrome. She was concerned that this was extremity referral pain from the lumbar spine. On physical examination, however, she had some swelling in the retro-Achilles bursa and there was marked tenderness over this on the right greater than on the left. Dr. Saal's impression was that her extremity pain was secondary to pre-Achilles bursitis and her back pain flare up was due to increasing stress from her exercises. Dr. Saal's plan was to carry out an intensive and focused rehabilitation program. Petitioner remained on temporary total disability until November 30, 2002. Id.

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[21] Marcaine is "trademark for preparations of bupivacaine hydrochloride." Dorland's at 1105. Bupivacaine hydrochloride is "a homologue of mepivacaine, chemically related to lidocaine, used as a local anesthetic for infiltration, peripheral nerve block, retrobulbar block, subarachnoid block, sympathetic block, and caudal and epidural anesthesia." Id. at 261.

[22] Decadron is "trademark for a preparation of dexamethasone." Dorland's at 474. Dexamethasone is "a synthetic glucocorticoid, 25 times as potent as cortisol: used topically on the skin and conjunctiva as an anti-inflammatory and administered orally in replacement therapy for adrenocortical insufficiency, as an anti-inflammatory and immunosuppressant in a wide variety of disorders, and as an antiemetic in cancer chemotherapy." Id. at 504.

[23] Depo-Medrol is "trademark for preparations of methyl-prednisolone acetate." Dorland's at 492. Methyl-prednisolone is "a synthetic glucocorticoid derived from progesterone, used in replacement therapy for adrenocortical insufficiency and as an anti-inflammatory and immunosuppressant in a wide variety of disorders." Id. at 1154.

On November 7, 2002, Dr. Saal reevaluated petitioner. Id. at 31. Petitioner's low back had a slight flare up from doing some hamstring strengthening exercise, but overall she was doing fairly well. Her ankle was significantly better although somewhat symptomatic after a local injection. Dr. Saal recommended orthotics and strengthening exercises. Petitioner remained on temporary total disability through December 30, 2002. Id.

On January 6, 2003, petitioner filled out a medical history for a chiropractor K. Robyn Kubo-Manley at Willow Chiropractic, stating she had the following medical history: neck pain, pain in her arms and legs, thyroid problems, and a lower back injury since 2000. Med. recs. Ex. 15, at 16.

On January 7, 2003, Dr. Saal reevaluated petitioner. Med. recs. Ex. 11, at 32. Petitioner said her symptoms persisted. Her exercise tolerance had improved, but she had a persistent limitation and inability to carry out any hip or leg extension. This caused increased back pain. She described a 50 percent reduction in symptom level. Dr. Saal pondered the etiology of petitioner's persistent low back pain and thought it could be residual discogenic pain at the L5-S1 vs. posterior element pain. He thought diagnostic therapeutic facet blocks were indicated. Petitioner remained on full temporary disability through March 3, 2003. Id.

On January 9, 2003, petitioner saw Dr. Su, complaining of continuing problems with her back. Med. recs. Ex. 12, at 29 (filed also as Ex. 69, at 33).

On January 28, 2003, petitioner had an MRI of her lumbar spine, to be compared to one done March 23, 2001 which had revealed mild disc disease at the L3-L4 and L5-S1 disc levels without evidence for herniation or transligamentous disc extrusion. Med. recs. Ex. 11, at 33. Dr. Murray A. Solomon's findings were there were no significant interval changes from the previous MRI. There was mild disc disease at the L4-L5 and L5-S1 disc levels without evidence for large herniation or transligamentous disc extrusion at either level. Id.

On February 7, 2003, petitioner saw Dr. Saal and told him she had a flare up with back pain centrally and bilaterally from doing scissor kicks in the pool. Id. at 23. Dr. Saal increased her Vioxx.[24] Id.

On February 11, 2003, petitioner saw Dr. Su, stating that Zoloft helped her somewhat and elevated her mood to some degree. She had an underactive thyroid. Dr. Su increased petitioner's dosage of Synthroid.[25] Med. recs. Ex. 69, at 34.

On February 13, 2003, petitioner saw Dr. Saal complaining of low back pain. Med. recs.

[24] Vioxx is "trademark for a preparation of rofecoxib." Dorland's at 2057. Rofecoxib is "a nonsteroidal anti-inflammatory drug of the COX-2 inhibitors groups, used in treatment of osteoarthritis, acute pain, and dysmenorrhea. . . ." Id. at 1652.

[25] Synthroid is "trademark for a preparation of levothyroxine sodium." Dorland's at 1856. Levothyroxine sodium is "the monosodium salt of L-thyroxine, the naturally occurring form of thyroxine, obtained from the thyroid gland of domesticated food animals or prepared synthetically. It is used as replacement therapy for hypothyroidism and in the prophylaxis and treatment of goiter and of thyroid carcinoma. . . ." Id. at 1032.

Ex. 11, at 35. Dr. Saal writes that her MRI scan showed no significant change compared to the one in 2001. She had degenerative changes only at L5-S1, which had not progressed. However, she had significant facet degenerative changes at those levels. On physical examination, petitioner had painful extension, worse on the right than on the left as well as in the center. Dr. Saal planned to carry out lumbar facet injections. Petitioner remained on temporary total disability through April 30, 2003. Id.

On March 7, 2003, Dr. Saal performed a lumbar intra-articular facet block on the right and left of L4-L5 and L5-S1. Id. at 36.

On April 3, 2003, Dr. Saal reevaluated petitioner. Id. at 39. Petitioner said she was 30 percent improved. She had marked dramatic improvement the day of the facet blocks which lasted approximately six hours following the anesthetic injection. This strongly suggested to Dr. Saal that facet symptoms and facet irritation played a role in generating her present pain. He proposed advancement in physical rehabilitation. Petitioner remained on temporary total disability through May 30, 2003. Id.

On April 24, 2003, Dr. Saal reevaluated petitioner. Id. at 40. She reported that her marked improvement in back pain and increased exercise tolerance had begun to wear off and she was approximately 40 percent worse than the best she had felt after the facet injections. Her symptoms were localized across her lower back and increased with extension, which was limited approximately 80 percent that day. Dr. Saal's impression was that petitioner had facet-related pain and would benefit from a median branch rhizotomy[26] if median branch diagnostic blocks were helpful. Id.

On May 23, 2003, Dr. Saal performed lumbar median nerve root blocks on the right and left of L3, L4, and L5. Id. at 41.

On June 19, 2003, Dr. Saal reevaluated petitioner. Id. at 43. Despite her marked relief in the corticosteroid and anesthetic phases with an intra-articular facet block, she had no or minimal response during the anesthetic phase of the median branch block. Dr. Saal considered whether petitioner had relative intolerance to local anesthetics since this was a low dose and volume vs. a non-discrete facet source of her symptoms. He considered this somewhat paradoxical. His recommendation was to repeat the median branch block with both short- and long-acting anesthetic and with a slightly higher volume, being careful of nonspecific spread. If the block were negative again, then petitioner was not a candidate for facet rhizotomy. However, she could be a candidate for further discogenic treatment considering her partially significant improvement, which was inadequate for carrying out full and usual work. Id.

On October 14, 2003, Dr. Saal performed lumbar intra-articular facet blocks on the right and left of L4-L5 and L5-S1. Id. at 44.

On November 13, 2003, Dr. Saal reevaluated petitioner. Id. at 47. Petitioner was

[26] Rhizotomy is "interruption of a cranial or spinal nerve root. . . ." Dorland's at 1641.

significantly improved from where she first started but was still limited compared to normal. She could carry out light housework and cook dinner and eat it, but she still could not do any heavy housework, repetitive bending, stooping or lifting. Her symptoms remained in her low back. On physical examination, she had limited lumbar extension by 50 percent and limited forward flexion by 50 percent. Dr. Saal's impression was that internal disc disruption and discogenic pain were the persistent source of her symptoms. He recommended she live with what she had or do a repeat discography. He prescribed a Lidoderm[27] patch. Id. Petitioner remained on temporary total disability through December 30, 2003. It was clear that she would not be able to return to her full and usual job duties as a nurse. Id.

On January 8, 2004, Dr. Saal reevaluated petitioner. Id. at 48. Dr. Saal suggested a lumbar discography to determine if the L4-L5 disc were painful or if the problem were the L5-S1 level. If that fails, she would be a candidate for a disc replacement or lumbar interbody fusion. He prescribed four treatments of acupuncture. Petitioner was on temporary total disability through March 1, 2004. Id.

On February 26, 2004, Dr. Saal reevaluated petitioner. Id. at 49. She reported continued symptoms. Dr. Saal's impression was internal disc disruption. Petitioner would continue on temporary total disability through March 30, 2004. Id.

On March 25, 2004, petitioner saw Dr. Saal to discuss her course to date. Id. at 50. She was somewhat worse and less functional. Dr. Saal thought petitioner was a candidate for either disc replacement or fusion. Id. Petitioner was on temporary total disability through May 30, 2004. Id.

On May 6, 2004, Dr. Saal reevaluated petitioner. Id. at 51. She was still waiting for a surgical consultation. Lumbar flexion on physical examination was 60 percent of normal. Lumbar extension was 20 percent of normal. Bilateral side bending was guarded at 75 percent of normal. Dr. Saal's impression was internal disc disruption at multiple levels. Petitioner was released to modified duties of no lifting greater than 10 pounds, a required posture change every 30 minutes, and no pushing or pulling greater than 50 pounds. Id.

On June 22, 2004, Dr. Saal saw petitioner for a long discussion after her consultation with Dr. Hsu. Id. at 52. Dr. Hsu recommended she have lumbar discography to determine what levels are painful and if there were a disc that could be treated with an IDET and if so to carry that out. If that procedure failed, she was a candidate for lumbar disc replacement surgery. Petitioner continued to have functionally limiting, impairing discogenic pain. Low back pain daily limited her ability to sit, stand, walk, or do any lifting or carrying. She remained on temporary total disability through August 1, 2004. Id.

On December 23, 2004, Dr. Saal wrote what he called his final report. Id. at 53.

[27] Lidoderm is "trademark for a preparation of lidocaine." Dorland's at 1034. Lidocaine is "a drug having anesthetic, sedative, analgesic, anticonvulsant, and cardiac depressant activities, used as a local anesthetic, applied topically to the skin and mucous membranes." Id.

Petitioner decided against aggressive surgery. Id. Petitioner described constant minimal to slight pain that became moderate with prolonged sitting of longer than 20 to 30 minutes, standing in one spot for longer than 15 minutes, or doing repetitive bending, stooping, or heavy lifting. Id. at 54. Rest and ice offered relief as did anti-inflammatory medication. Physical examination showed a 25 percent decrease in lumbar forward flexion and a 50 percent decrease in lumbar extension. She had full bilateral lateral side bending. She could carry out her duties as a nurse if accommodations were made for postural changes and she was precluding from heavy lifting and repetitive bending. Id.

On February 3, 2005, Dr. Saal reevaluated petitioner. Id. at 56. She decided she did not want to live with her back condition and needed to do something else. Dr. Saal's impression was discogenic pain. Petitioner was ready to undergo surgery. Id.

On March 24, 2005, Dr. Saal reevaluated petitioner. Id. at 57. She reported her symptoms unchanged. Id. He recommended another IDET. Id. at 58.

On June 7, 2005, Dr. Saal reevaluated petitioner. Id. at 61. Her symptoms were unchanged. He recommended a lumbar discography. Id. Petitioner was to be off work until August 10, 2005. Id. at 62.

On August 9, 2005, Dr. Saal reevaluated petitioner. Id. at 63. She continued to complain of functionally limiting low back pain. A recent MRI of her bilateral ankles showed evidence of adhesion of the peritendinous sheath around the Achilles tendon with a recommendation of treatment with saline by Dr. Fred Orcutt or potentially surgery. Dr. Saal recommended discography. Id. Petitioner was off work until October 1, 2005. Id. at 64.

On September 20, 2005, Dr. Saal reevaluated petitioner. Id. at 65. Her symptoms remained the same. She still had sitting and bending pain and had difficulty carrying out intensive therapeutic exercises because of a flare up of her symptoms. He recommended she return to modified duty with no lifting greater than 25 pounds and no repetitive bending, stooping, or twisting. She required postural changes every 30 minutes. She could push only 100 pounds and pull only 50 pounds. Id.

On December 13, 2005, Dr. Saal reevaluated petitioner. Id. at 67. She reported her symptoms were somewhat worse. They were in her low back and bilateral heels. A new MRI scan did not show significant abnormalities. She had undergone a number of laboratory tests so that Dr. Orcutt[28] could exclude the possibility that she had rheumatic disease or multiple myeloma.[29] She had a loss of thigh circumference. Id. Petitioner was to be off work until

[28] The undersigned cannot find any records from Dr. Orcutt filed in this case. On November 5, 2018, the undersigned ordered petitioner to file them, but petitioner filed a status report on November 15, 2018, stating that Dr. Fred Orcutt, an orthopedic surgeon, retired and all reports from 2010 and earlier were unavailable. Petitioner filed exhibit 120, a statement from the medical group to which Dr. Orcutt previously belonged, to that effect.

[29] Multiple myeloma is "a disseminated type of plasma cell dyscrasia characterized by multiple bone marrow tumor foci and secretion of an M component, associated with widespread osteolytic lesions resulting in bone pain, pathologic fractures, hypercalcemia, and normochromic normocytic anemia. . . ." Dorland's at 1219.

January 30, 2006. Id. at 68.

On February 9, 2006, Dr. Saal reevaluated petitioner. Id. at 69. She reported a marked increase in the level of pain in her legs, worse in the past two weeks. She had difficulty sleeping at night. She underwent a new MRI scan and an EMG study. On physical examination, positive straight leg raising on both sides at 60 degrees caused leg and back pain. Dr. Saal's impression was referred pain into the lower extremities related to a degenerative painful disc that has disc disruption/annulus tear at L5-S1. Id. Petitioner was to be off work until April 1, 2006. Id. at 70.

On March 9, 2006, Dr. Saal reevaluated petitioner. Id. at 71. She had improvement in her leg pain with use of Lyrica.[30] Id.

On March 29, 2006, petitioner noted neck and arm pain intermittently with numbness in her right hand three fingers (3rd, 4th, and 5th digits) since 2003. Med. recs. Ex. 15, at 18. She had had neck and arm pain for six months. Id. at 15.

On March 30, 2006, Dr. Saal reevaluated petitioner. Med. recs. Ex. 11, at 72. Her symptoms remained the same. She was on total temporary disability through May 5, 2006. Id.

On April 25, 2006, Dr. Saal reevaluated petitioner. Id. at 73. She continued to complain of the same symptoms. She went off Lyrica because of weight gain. She had returned to work with no lifting greater than 20 pounds, no pushing or pulling greater than 40 pounds and only occasional bending, no climbing, and no prolonged standing. Postural changes were required every thirty minutes. Id.

On April 3, 2007, Dr. Saal reevaluated petitioner. Id. at 75. Petitioner said she had made a 75-80 plus percent improvement. She could tolerate sitting and standing for hours. Her back pain was less intense. Dr. Saal opined she could return to her full and usual work duties. Id.

On November 21, 2007, petitioner complained of left shoulder pain that had been bothering her for 2-3 months. Med. recs. Ex. 14, at 49. It was not getting better despite chiropractic treatment, upper body strengthening, anti-inflammatories, and swimming two to four times a week. On physical examination, petitioner was tender anteriorly overlying the biceps tendon. The doctor sent petitioner to another doctor for an injection. Id.

On March 3, 2008, petitioner saw Dr. Mary Regan at Samaritan Family Practice, complaining of one month of aching in her fingers and thumbs bilaterally and head and chest congestion for three days. Id. at 45. Petitioner needed a work note since she missed the last several days due to cold/flu. Petitioner was seeing a chiropractor but that seemed to be making her worse. Petitioner had intermittent pain on her right side. Dr. Regan questioned whether

[30] Lyrica is "trademark for a preparation of pregabalin." Dorland's at 1088. Pregabalin is "a derivative of γ-aminobutyric acid (GABA) having anticonvulsant and antinociceptive effects, used in the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia. . . ." Id. at 1509. "Antinociceptive" means "blocking or reducing sensitivity to painful stimuli. . . ." Id. at 108.

petitioner's fingers were slightly swollen. She noted that petitioner had a family history of rheumatoid arthritis in her grandmother. Id. Petitioner's physical examination was unremarkable except for mild nasal congestion. Dr. Regan diagnosed petitioner with upper respiratory infection, cervical pain, and hand pain. She referred petitioner for testing to see if she had a positive ANA[31] and rheumatoid factor ("RF").[32] Id. Petitioner had a positive ANA of 1:160. Id. at 20. Dr. Regan noted petitioner might have a rheumatic disorder, discussed this with petitioner, and referred her to a rheumatologist.[33] Id.

On that same date, March 3, 2008, Dr. Keith Fraker did x-rays on petitioner's cervical spine for persistent neck pain. Id. at 2. Petitioner had degenerative change at the C5-C6 level with anterior and posterior spurring and disc space narrowing. C6 and C7 appeared to be fused, which Dr. Fraker assumed to be a congenital anomaly. He noted degenerative changes over the facet joints and joints of Luschka.[34] There might be some neural foraminal encroachment at the C5 level, especially on the right. He noted calcification within the ligamentum nuchae and some reversal of the normal cervical curve. Id.

On March 5, 2008, petitioner's erythrocyte sedimentation rate ("ESR")[35] was normal, her rheumatoid factor serum was negative, but her antinuclear antibody ("ANA") was positive at 1:160 with a homogeneous pattern.[36] Id. at 20.

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[31] Antinuclear antibodies (ANA) are "antibodies directed against nuclear antigens; ones against a variety of different antigens are almost invariably found in systemic lupus erythematosus and are frequently found in rheumatoid arthritis, scleroderma (systemic sclerosis), Sjögren syndrome, and mixed connective tissue disease. Antinuclear antibodies may be detected by immunofluorescent staining. Serologic tests are also used to determine antibody titers against specific antigens." Dorland's at 101.

[32] Rheumatoid factor ("RF") are "antibodies directed against antigenic determinants, i.e., Gm, in the Fc region of the IgG class of immunoglobulins; these are found in the serum of about 80 percent of persons with classical or definite rheumatoid arthritis, but only about 20 percent of those with juvenile rheumatoid arthritis. Rheumatoid factors may be of the IgM, IgG, or IgA classes of immunoglobulins, although serologic tests measure only IgM. Rheumatoid factors also occur in other connective tissue diseases and infectious diseases, such as Sjögren syndrome, systemic lupus erythematosus, sarcoidosis, subacute bacterial endocarditis, hepatitis A, and leprosy." Dorland's at 676.

[33] The undersigned cannot find any rheumatology records from 2008. In an Order dated November 5, 2018, the undersigned ordered petitioner to file them, but petitioner filed a status report on November 15, 2018, stating the rheumatologist, Dr. Carter V. Multz of the Arthritis Care Center in San Jose, was dead. Petitioner filed as exhibit 119 an obituary of Dr. Multz, stating his date of death was August 7, 2013.

[34] Joints of Luschka are "a series of jointlike structures at the lateral edges of the vertebral bodies from vertebra C3 to T1, forming small spurlike lips at the upper surface, covered with cartilage, and containing a capsule filled with fluid. They are considered by some to be true diarthrodial joints, and by others to be degenerative spaces of the intervertebral disks filled with extracellular fluid and lined by a membrane formed by fibrocytes. They are frequent sites of spur formation. Called also *uncovertebral j's*." Dorland's at 973.

[35] Erythrocyte sedimentation rate ("ESR") is "the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood, measured by the distance the top of the column of erythrocytes falls in a given time interval under specified conditions; an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins, which decrease the zeta potential on erythrocytes by dielectric shielding and thus promote rouleau formation. It is increased in monoclonal gammopathy, hypergammaglobulinemia due to inflammatory disease, hyperfibrinogenemia, active inflammatory disease, and anemia." Dorland's at 1594. Rouleau formation is "the aggregation of erythrocytes in structures resembling piles of coins, caused by adhesion of their flat surfaces." Id. at 733.

[36] "ANAs are used to diagnose systemic lupus erythematosus (SLE) and other autoimmune diseases." Kathleen D.

On March 12, 2008, petitioner saw MR (presumably "Mary Regan") at Samaritan Family Practice, complaining that her head and ear congestion persisted. Id. at 44. Petitioner said she could not "shake this cold." Id. Dr. Regan diagnosed petitioner with sinusitis and prescribed Augmentin.[37] Id.

On May 20, 2009, Dr. Saal reevaluated petitioner. Med. recs. Ex. 11, at 77. Petitioner was taking Cymbalta[38] and discontinued Zoloft.[39] She lived a full and active lifestyle. Id.

On September 22, 2009, petitioner saw a doctor ("TK") at Samaritan Family Practice, stating she fell in the lobby of a Las Vegas hotel on September 18, 2009 and landed on her right hip and right elbow and arm. Med. recs. Ex. 14, at 37. She had a stiff neck and lower back with slight numbness in her arms and legs, but no weakness. The doctor diagnosed cervical and lumbar strain, recommended rest, ice, and heat, and referred petitioner for physical therapy. Id.

On October 14, 2009, petitioner received flu vaccine[40] in her left deltoid from Dr. Joceliza G. Chaudhary at Samaritan Family Practice. Id. at 35. This occurred during petitioner's office visit for a urinary tract infection and allergic rhinitis. Id. at 36. Petitioner did not have a reaction to the October 14, 2009 flu vaccination.

On November 20, 2009, petitioner saw a doctor ("MR" presumably Mary Regan) at Samaritan Family Practice, complaining of a sore throat and bilateral ear pain for three days, and 99.4 degree temperature two hours previously. Id. at 34. One week earlier, she developed body

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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 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. Petitioner tested negative in 2008 and 2012 for RF. Petitioner tested negative in 2012 for ssDNA.

[37] Augmentin is "trademark for combination preparations of amoxicillin and clavulanate potassium." Dorland's at 179. Amoxicillin is "a semisynthetic derivative of ampicillin effective against a broad spectrum of gram-positive and gram-negative bacteria; used especially in the treatment of infections due to susceptible strains of *Haemophilus influenzae, Escherichia coli, Proteus mirabilis, Neisseria gonorrhoeae*, streptococci (including *Streptococcus faecalis* and *S. pneumonia*), and nonpenicillinase-producing staphylococci." Id. at 65.

[38] Cymbalta is "trademark for a preparation of duloxetine hydrochloride." Dorland's at 457. Duloxetine hydrochloride is "a serotonin-norepinephrine reuptake inhibitor, used for the treatment of major depressive disorder and the relief of pain in diabetic neuropathy. . . ." Id. at 572.

[39] Zoloft is "trademark for preparations of sertraline hydrochloride." Dorland's at 2092. Sertraline hydrochloride is "a selective serotonin reuptake inhibitor, used to treat depressive, obsessive-compulsive, and panic disorders. . . ." Id. at 1699.

[40] In the 2009-2010 flu season, the trivalent flu vaccine contained A/Brisbane/59/2007-like virus (H_1N_1), A/Brisbane/10/2007-like virus (H_3N_2), and B/Brisbane/60/2008-like virus (B/Victoria lineage). Update: Influenza Activity – United States, September 28, 2008—April 4, 2009, and Composition of the 2009—10 Influenza Vaccine, 58 MORBIDITY AND MORTALITY WEEKLY REPORT (MMWR) 14:369-74 (April 17, 2009), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5814a4.htm.

aches, and fever which resolved in 3-4 days. Three days earlier, she developed sinus pain with discharge, sore throat, and hoarseness. She wanted Vicodin for sleep. Dr. Regan diagnosed petitioner with an upper respiratory infection and pharyngitis. She prescribed Vicodin. Id.

On March 11, 2010, petitioner saw a doctor ("JH") at Samaritan Family Practice, complaining of hot flashes and sweating. Id. at 29. She stated she was ready to stop smoking. She wanted to stop taking Cymbalta, which she had taken for back pain which had now resolved.

On January 20, 2011, petitioner saw a doctor ("TK") at Samaritan Family Practice to evaluate her thyroid. Id. at 28. She had been fatigued for 1-2 months. She had had right shoulder pain and trouble lifting her arm for 2-3 months. She had trouble sleeping on her right side. She requested physical therapy and the doctor referred her for it. Id.

On March 17, 2011, petitioner saw a doctor at Samaritan Family Practice, complaining of foot and shoulder pain. Med. recs. Ex. 14, at 27. She needed a referral for physical therapy again. She did not go to physical therapy when referred before and the last referral expired. Her palpitations resolved and she discontinued Sudafed. The doctor diagnosed petitioner with right foot pain, right shoulder strain, hypothyroidism, and neuropathy. Id.

On April 8, 2011, petitioner saw a doctor ("TH") at Samaritan Family Practice because she had a rash on her stomach since the day before and a burning sensation. Id. at 26. The doctor diagnosed dermatitis, probably due to sitting in a hot tub while wearing an old swimsuit. Id.

On June 15, 2011, petitioner saw a doctor ("TK") at Samaritan Family Practice for two reasons: (1) she had sliced her pinkie finger the prior evening, and (2) her right shoulder had been painful for nine months. Id. at 25.

On January 26, 2012, petitioner saw Dr. Jing Qing Xu as a new patient. Med. recs. Ex. 3, at 1. Dr. Xu was at Kaiser Permanente Medical Group in San Jose, CA. Id. Petitioner had chronic pain syndrome and shoulder joint pain. Dr. Xu prescribed Cymbalta for chronic pain syndrome. Id. at 3. Petitioner had chronic left shoulder pain. Id. Petitioner was on levothyroxine for hypothyroidism, Benicar,[41] and Cymbalta. Id.

On March 16, 2012, Dr. Xu called petitioner. Id. at 20. She said over the prior three to four days, she had been feeling acid reflux, burped a lot, and felt something stuck in her esophagus. She had been taking ranitidine.[42] Dr. Xu diagnosed petitioner with GERD[43] and prescribed Omeprazole,[44] told her to avoid citrus, and advised walking and stress reduction. Id.

[41] Benicar is "trademark for a preparation of olmesartan medoxomil." Dorland's at 208. Olmesartan medoxomil is "a selective angiotensin receptor antagonist used as an antihypertensive . . . ." Id. at 1319.
[42] Ranitidine is "a histamine H_2 receptor antagonist, which inhibits gastric secretion." Dorland's at 1592.
[43] GERD is "gastroesophageal reflux disease." Dorland's at 772.
[44] Omeprazole is "a proton pump inhibitor used in the treatment of dyspepsia, gastroesophageal reflux disease, and gastric hypersecretory conditions. . . ." Dorland's at 1319.

On August 13, 2012, petitioner saw Dr. Xu, telling Dr. Xu that she had pain in her left arm and right shoulder intermittently for a long time. Id. at 33. Dr. Xu diagnosed petitioner with impingement syndrome of the shoulder. Id. In Dr. Xu's progress notes, the doctor says that petitioner has complained of pain intermittently in both shoulders. Id. at 34. Petitioner had positive kiss elbow signs. Id. Petitioner worked as a registered nurse at the Intensive Care Unit, pushing carts around. Dr. Xu's diagnosis was impingement syndrome of the shoulders. Id.

Postvaccination Records

On September 20, 2012, petitioner received flu vaccine[45] in her left deltoid. Med. recs. Ex. 16, at 2.

On October 3, 2012, petitioner saw Dr. Xu complaining of still having pain in her joints, knees, hands, and lower back, but her shoulder pain was improving. Med. recs. Ex. 3, at 37. Dr. Xu diagnosed petitioner with chronic sinusitis and osteoarthritis of the hand. Id. at 36. Both her hands had slight swelling. Id. at 37. Cyclic citrullinated peptide ("CCP")[46] for rheumatoid arthritis was negative at 5 (being less than 20). Id. at 40. RF factor was negative at 10.3 (reference range less than 14.0). Id. C-reactive protein ("CRP")[47] was negative at 0.4 (reference range less than 0.5). Id. at 41. Petitioner's Nuclear AB Panel testing on October 3, 2012 (Ex. 3, at 41) was negative for all of the following: dsDNA antibody[48]; Sjögrens[49]-A (anti-SS-A) antibody and –B (anti-SS-B) antibody; Smith IgG; chromatin (nucleosomal) antibody; ribosomal P antibody; centromere antibody; Sm antibody+RNP antibody; Scl-70 antibody; and Jo-1 antibody. Id. Her RNP antibody was positive at 1.2 (when the normal result is less than 1.0). Id.

On October 15, 2012, petitioner had a positive ANA of 2+ with homogeneous staining

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[45] In the 2012-2013 flu season, the trivalent flu vaccine contained A/California/7/2009-like virus (pH_1N_1), A/Victoria/361/2011-like virus (H_3N_2), and B/Wisconsin/1/2010-like virus (B/Yamagata lineage). Update: Influenza Activity – United States, 2011-12 Season and Composition of the 2012-13 Influenza Vaccine, 61 MORBIDITY AND MORTALITY WEEKLY REPORT (MMWR) 22:414-20 (June 8, 2012), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6122a4.htm. The "p" before the "H" (hemagglutinin) stands for "pandemic." Robert P. de Vries et al., Evolution of the Hemagglutinin Protein of the New Pandemic H1N1 Influenza Virus: Maintaining Optimal Receptor Binding by Compensatory Substitutions, 87 J VIROL 24: 13868-877, 13868 (2013).

[46] Cyclic citrullinated peptide ("CCP") is "a synthetic, citrulline-containing peptide with a cyclic structure, used in assays for rheumatoid arthritis; the presence of antibodies to this peptide is highly specific for rheumatoid arthritis." Dorland's at 1408.

[47] C-reactive protein ("CRP") is "a globulin that forms a precipitate with the somatic C-polysaccharide of the pneumococcus in vitro; it is the most predominant of the acute phase proteins." Dorland's at 1532.

[48] Anti-dsDNA antibody is "a type of antinuclear antibody specific for double-stranded DNA, found in the serum of patients with systemic lupus erythematosus." Dorland's at 100.

[49] Sjögren syndrome is "a symptom complex of unknown etiology, usually occurring in middle-aged or older women, marked by the triad of keratoconjunctivitis sicca with or without lacrimal gland enlargement, xerostomia with or without salivary gland enlargement, and the presence of a connective tissue disease, usually rheumatoid arthritis but sometimes systemic lupus erythematosus, scleroderma, or polymyositis. An abnormal immune response has been implicated." Dorland's at 1848.

and a titer of 1:320. Id. at 45. Her ESR was normal. Id. at 46.

On October 31, 2012, petitioner saw Dr. Jan Jingyang Lin, a rheumatologist, complaining of joint pain in her hands, knees, and toes with prolonged morning stiffness for many months.[50] (This would place onset of petitioner's pain and prolonged morning stiffness before the flu vaccination which was just six weeks earlier than petitioner's October 31, 2012 visit to Dr. Lin.) Med. recs. Ex. 13, at 96-99. Dr. Lin was at Kaiser Permanente Medical Group in San Jose, CA. Med. recs. Ex. 3, at 48. Petitioner had a history of redness of face and nasal bridge and chin, dry eyes and mouth, and extreme fatigue. On physical examination, she had bilateral proximal-interphalangeal ("PIP") and metacarpal-phalangeal ("MCP") joint tenderness, ulnar deviation, and bilateral knee tenderness. Dr. Lin's diagnosis was MCTD.[51] She started petitioner on hydroxychloroquine[52] and prednisone. Id. at 47-64. Dr. Lin tested petitioner for cardiolipin antibody[53] and for lupus anticoagulant, both of which were negative. Id. at 62. However, petitioner's cardiolipin IgG was 28, which was high since the normal range is 1-14, and her cardiolipin IgM was 15, which was also high since the normal range is 1-11. Id. at 63. Dr. Lin had petitioner undergo chest x-rays to look for interstitial lung disease, and the result was normal. Id. at 64. Her ESR and CRP on October 31, 2012 were normal. Id. at 58, 59. Petitioner's C3 and C4 complement levels were normal. Id. at 60.

On January 7, 2013, petitioner saw Dr. Lin. Her joint symptoms had resolved on steroids, but returned while she was on hydroxychloroquine. She complained of muscle pains. Her joint tenderness remained. She mentioned her joints were swollen. Dr. Lin prescribed methotrexate ("MTX").[54] Id. at 67-70.

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[50] Subsequently, on June 19, 2015, two years and seven and one-half months after October 31, 2012, Dr. Lin "corrected" this history at the urging of petitioner by writing a request on June 7, 2015 that Dr. Lin change the onset date of her joint pains to "several weeks." Med. recs. Ex. 10, at 1. But on June 19, 2015, Dr. Lin changed the onset of petitioner's joint pains not to "several weeks" but to "two months since August 2012." Med. recs. Ex. 108, at 11. This still placed onset before the September 20, 2012 flu vaccination. On January 5, 2016, three years and two months after petitioner saw Dr. Lin on October, 31, 2012, Dr. Lin "corrected" this initial history a second time at the urging of petitioner to reflect an onset of "four weeks since the end of September 2012." Med. recs. Ex. 108, at 11. Now, the onset was after the September 20, 2012 flu vaccination.

[51] Mixed connective tissue disease ("MCTD") is "a disorder combining features of scleroderma, myositis, systemic lupus erythematosus, and rheumatoid arthritis, and marked serologically by the presence of antibody against extractable nuclear antigen." Dorland's at 539.

[52] The trademark for hydroxychloroquine sulfate is Plaquenil. Dorland's at 1456. Hydroxychloroquine sulfate is "a 4-aminoquinoline compound with antiprotozoal and anti-inflammatory properties, used for suppression and treatment of malaria, for suppression of lupus erythematosus, and as an anti-inflammatory disease-modifying antirheumatic drug in treatment of rheumatoid arthritis. . . ." Id. at 881.

[53] Anticardiolipin antibody is "an antibody directed against cardiolipin, seen with increased frequency in systemic lupus erythematosus; its presence correlates with increased risk for thrombotic events." Dorland's at 100.

[54] Methotrexate ("MTX") is "a folic acid antagonist that acts by inhibiting synthesis of DNA, RNA, thymidylate, and protein; used as an antineoplastic in treatment of a wide variety of malignancies, including acute lymphocytic, meningeal, and acute myelocytic leukemia; gestational choriocarcinoma; chorioadenoma destruens; hydatidiform mole; carcinoma of the breast, lung, and head and neck; non-Hodgkin lymphomas; mycosis fungoides; and osteosarcoma. . . . It is also used as an antipsoriatic and antiarthritic in the treatment of severe, recalcitrant, disabling psoriasis and severe rheumatoid and psoriatic arthritis." Dorland's at 1151.

On March 4, 2013, petitioner saw Dr. Lin. On physical examination, petitioner had swollen joints. Dr. Lin increased petitioner's dosage of MTX and tapered her steroids. Id. at 74-83. Dr. Lin rechecked petitioner's ESR and CRP on March 4, 2013. They were normal. Id. at 80. Dr. Lin also rechecked petitioner's cardiolipin IgG and IgM on March 4, 2013 and they were both normal. Id. at 82-83.

On May 14, 2013, petitioner's CRP was slightly elevated at 0.7 when the normal range is at or below 0.5. Id. at 87. Her ESR was still normal. Id. Petitioner's C4 complement was high at 45.6 when the normal range is 10.0 to 40.0. Id. at 88. Petitioner's C3 complement was also high at 202 when the normal range is 83 to 180. Id. at 89.

On May 15, 2013, petitioner saw NP Cynthia A. Liu, in gynecology. Id. at 90. Petitioner told NP Liu that she had been diagnosed with RA, lupus, and Sjögren's. Id. at 91. She complained of chronic pain mostly in her knees and hands, but stated "everything hurts." Id. She complained of frequent hot flashes and sweating. Id. NP Liu noted petitioner had been diagnosed with GERD on March 16, 2012. Id. at 93.

On May 17, 2013, petitioner saw Dr. Lin. Petitioner complained of pain in her PIP and MCP joints with swelling. She had skin thickness on her fingers resembling sclerodactyly.[55] Dr. Lin prescribed tumor necrosis factor ("TNF")-inhibitor therapy for her inflammation (etanercept).[56] Id. at 98-101.

On May 30, 2013, petitioner saw Dr. Yuhjung John Tsai, an allergist, who noted she had an allergic reaction to flu vaccinations in 1999 and 2012. Id. at 107, 109. Dr. Tsai was at Kaiser Permanente Medical Group at San Jose, CA. After petitioner's flu vaccination on October 7, 2009,[57] she had a large bruise and mass on her shoulder extending down the left arm with development of frozen shoulder the following week. Id. at 107. She started having migraines afterwards. In six months, her symptoms improved and she did not have any more migraines. She did not receive any more flu vaccinations until the county medical director indicated in August 2012 the importance of receiving flu vaccine. After her 2012 flu vaccination, in October, she developed weakness and shortness of breath with no previous history of rheumatoid conditions. She saw a rheumatologist Dr. Lin who diagnosed MCTD. Id. She told Dr. Tsai that she had quit smoking one month earlier, or April 2013. Id. at 109. Dr. Tsai advised petitioner to

[55] Sclerodactyly is "localized scleroderma of the digits, as in acrosclerosis." Dorland's at 1679. Acrosclerosis is "a type of systemic scleroderma of the hands and feet, especially the digits (sclerodactyly), as well as the face and neck, in combination with Raynaud phenomenon." Id. at 21. Raynaud phenomenon is "intermittent bilateral ischemia of the fingers, toes, and sometimes ears and nose, with severe pallor and often paresthesias and pain, usually brought on by cold or emotional stimuli and relieved by heat; it is usually due to an underlying disease or anatomical abnormality." Id. at 1430.

[56] Etanercept is "a soluble tumor necrosis factor receptor that inactivates tumor necrosis factor, used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. . . ." Dorland's at 650.

[57] Dr. Tsai initially wrote petitioner received flu vaccine in 2009, but corrected this to 1999 in an addendum dated June 26, 2015. Med. recs. Ex. 108, at 27. He made this change at the request of petitioner. Med. recs. Ex. 13, at 212. Petitioner's medical records show that she had left supraspinatus tendinitis after the flu vaccine she received in her left arm on October 7, 1999. Med. recs. Ex. 69 at 1, 2, 4. She did not however have a reaction to the flu vaccine she received in her left arm on October 14, 2009. Med. recs. Ex. 14, at 35.

avoid all flu vaccinations. Id. at 110. He noted she did not have any history to suggest immunodeficiency. Id. Dr. Tsai wrote petitioner's symptoms were delayed and not characteristic of an IgE-mediated drug reaction. Id.

On July 12, 2013, petitioner saw MA Carmen Santana with swelling in her knuckles. Id. at 112.

On August 7, 2014, petitioner's ESR and CRP were normal. Id. at 119. Her C4 complement and C3 complement were normal. Id. at 120-21.

On August 19, 2013, petitioner saw Dr. Lin. Since she started etanercept, her joint symptoms were better. She complained of hair loss. On physical examination, petitioner had tender finger joints and knees, swelling in one PIP joint, synovitis in the left third PIP joint, and skin thickening of her fingers. Dr. Lin told petitioner to stop taking MTX due to hair loss, start Leflunomide[58] (anti-rheumatic drug), and use Voltaren[59] cream (anti-inflammatory). Id. at 125-28. Dr. Lin noted petitioner did not have Raynaud's phenomenon.[60] Id. at 125.

On October 31, 2013, petitioner's ESR and CRP were normal. Id. at 130-31. Her C4 complement and C3 complement were also normal. Id. at 132,

On November 25, 2013, petitioner saw Dr. Anna Graziella Barbara because of snoring. Id. at 141. Petitioner said she was often tired during the day and had to take a nap. Id. Dr. Barbara suggested petitioner take a sleep study to rule out obstructive sleep apnea. Id. at 143.

On January 6, 2014, petitioner saw Dr. Lin. Her joint tenderness continued but not the swelling since she started etanercept. She had ulnar deviation which was noted before since October 31, 2012. Dr. Lin had petitioner taper her steroids, and considered switching DMARD (disease-modifying antirheumatic drug) treatment to abatacept[61] or tocilizumab.[62] Id. at 141-55. Dr. Lin was not seeing any synovitis.[63] Id. at 149. Petitioner wanted Dr. Lin to sign a statement

[58] Leflunomide is "an immunomodulator that inhibits pyrimidine synthesis, used as a disease-modifying antirheumatic drug in treatment of rheumatoid arthritis. . . ." Dorland's at 1017.

[59] Voltaren is "trademark for preparations of diclofenac sodium." Dorland's at 2070. Diclofenac is "a nonsteroidal anti-inflammatory drug derived from phenylacetic acid." Id. at 513. Diclofenac sodium is "the sodium salt of diclofenac . . . in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis and also for a variety of nonrheumatic inflammatory conditions." Id.

[60] Raynaud phenomenon is "intermittent bilateral ischemia of the fingers, toes, and sometimes ears and nose, with severe pallor and often paresthesias and pain, usually brought on by cold or emotional stimuli and relieved by heat; it is usually due to an underlying disease or anatomical abnormality. When it is idiopathic or primary it is called *Raynaud disease*." Dorland's at 1430; see also 542.

[61] Abatacept is "a synthetic fusion protein produced by recombinant technology, comprising the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) linked to a portion of human immunoglobulin G1 (IgG1), which acts as an inhibitor of T-cell activation; used in the treatment of moderate to severe rheumatoid arthritis unresponsive to other medications, administered intravenously." Dorland's at 1.

[62] Tocilizumab is trademark for Actemra. https://www.actemra.com/ra/consider-actemra/actemra-works-differently.html (last visited October 19, 2018). It blocks the action of a protein called interleukin-6 (IL-6). Id.

[63] Synovitis is "inflammation of a synovium; it is usually painful, particularly on motion, and is characterized by a

for petitioner to extend her disability which Dr. Lin did. Id. Petitioner was on modified work from February 1, 2014 to December 31, 2014. Id. at 150. On January 6, 2014, petitioner's ESR and CSP were normal. Id. at 151-52. Her C4 complement and C3 complement were normal. Id. at 153.

On March 27, 2014, petitioner's ESR and CRP were normal. Id. at 158. Her C4 complement and C3 complement were also normal. Id. at 160.

On March 28, 2014, petitioner saw Dr. Lin to extend her disability. Id. at 162-63. Petitioner's joints were tender but not swollen. Dr. Lin noted again her ulnar deviation and sclerodactyly. Petitioner did not have Raynaud's phenomenon. Dr. Lin told petitioner to stop taking etanercept and switch to abatacept because she was concerned petitioner had a lupus component to MCTD. Id. at 163-66.

On April 8, 2014, petitioner had x-rays to rule out interstitial disease. Id. at 176. The results were normal. Id.

On June 12, 2014, Dr. Lin switched petitioner to leflunomide. Id. at 180-82. On June 12, 2014, petitioner's ESR and CRP were normal. Id. at 180.

On September 25, 2014, petitioner's ESR and CRP were normal. Id. at 184. Her C4 complement and C3 complement were also normal. Id. at 186.

On November 19, 2014, petitioner saw Dr. Lin who started her on tocilizumab. Id. at 190-94. In the range of systems, Dr. Lin noted petitioner did not have sclerodactyly or Raynaud's phenomenon. Id. at 192. Yet in her assessment and plan, Dr. Lin wrote petitioner had arthritis and Raynaud's phenomenon currently. Id. at 194.

On December 8, 2014, petitioner saw Dr. Golara Honari, a dermatologist, for telangiectasia[64] and subtle erythema on her cheeks and nose, sparing the bridge of her nose, with keratotic[65] papules on the sides of her face. Dr. Honari diagnosed petitioner with rosacea[66] and keratosis pilaris[67] rubra faceii. Med. recs. Ex. 13, at 409-11.

On June 7, 2015, petitioner wrote to Kaiser Permanente San Jose Medical Center requesting a correction of her records. Petitioner did not file this request, but did file the response from Kareem Olateju, Compliance Consultant, Corporate Compliance Department, Kaiser Permanente San Jose Medical Center, dated June 29, 2015. Med. recs. Ex. 10, at 1. This

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fluctuating swelling due to effusion within a synovial sac." Dorland's at 1856.

[64] Telangiectasia is "permanent dilation of preexisting small blood vessels (Capillaries, arterioles, venules) to form focal, discolored lesions, usually in the skin or mucous membranes." Dorland's at 1878.

[65] Keratosis is "any horny growth. . . ." Dorland's at 982.

[66] Rosacea is "a chronic skin disease, usually involving the middle third of the face, characterized by persistent erythema and often by telangiectasia with acute episodes of edema, papules, and pustules. . . ." Dorland's at 1654.

[67] Keratosis pilaris is "a common, benign condition in which hyperkeratosis occurs around hair follicles, usually on the extensor surfaces of the thighs and arms, but sometimes elsewhere. . . ." Dorland's at 982.

was after petitioner filed her petition pro se on March 13, 2015, but before she retained counsel on August 11, 2015. The letter from Kareem Olateju in response to petitioner states as follows:

> **AMENDMENT REQUEST:**
>
> That Dr. Yuhjung J. Tsai should amend your medical record to state that the Mixed Connective Tissue Disease you developed was a result of the flu shot you received and also to amend the date of a flu shot that you received from 10/7/2009 to 10/7/1999. You also requested from Dr. Jan J. Lin to correct her statement in your medical record regarding the duration of a condition you experienced to "several weeks."
>
> **RESPONSE:** Dr. Tsai reviewed your request including your medical record and **denied your request regarding the cause of the Mixed Connective Tissue Disease** but agreed to change the date you had a flu shot as requested. Dr. Lin also reviewed your request including your medical record and agreed with your request to change the duration of your condition to "several weeks." [emphasis added.]

On June 10, 2015, petitioner saw Dr. Xu, complaining of foot numbness for two months. Dr. Xu diagnosed peripheral neuropathy. Id. at 587-91.

On June 19, 2015, Dr. Lin "corrected" her records as to onset of petitioner's developing symmetric joint pains of bilateral hands, knees, and toes, associated with prolonged morning stiffness for **two months since August 2012**. Med. recs. Ex. 108, at 11. (In the original record of Dr. Lin dated October 31, 2012, five weeks after flu vaccination, she wrote the onset of petitioner's symmetric joint pains of bilateral hands, knees, and toes, associated with prolonged morning stiffness was **many months**. Med. recs. Ex. 8, at 48.)

On January 5, 2016, Dr. Lin again "corrected" her records as to onset of petitioner's developing symmetric joint pains of bilateral hands, knees, and toes, associated with prolonged morning stiffness for **four weeks since the end of September 2012**. Med. recs. Ex. 108, at 11.

Also on January 5, 2016, petitioner saw Dr. Lin for a medical visit. Med. recs. Ex. 10, at 1. Petitioner still had a lot of pain in the PIPs associated with tightness of her fingers and a lot of stiffness in her fingers and knees. Id. Petitioner did not have Raynaud's phenomenon. Id. Dr. Lin diagnosed petitioner with MCTD, and decided to raise her Actemra dose. Id. at 5. (These records are also filed as Exhibit 86, at 9-14.)

In a letter dated January 19, 2016 to Kaiser Permanente, petitioner's subject was "Corrections to Errors in My Medical Records." Med. recs. Ex. 112, at 1. She writes:

As a result of research that I have done to support my vaccine compensation program claim (National Vaccine Injury Compensation Program Claim No. 15-260V) I have become aware of several errors in my medical records. It is important that that [sic] these errors are corrected, not only for the purpose of the claim but also to set the record straight regarding my past and current health status.

1. On page 48 of my medical records (Exhibit 3 of the vaccine claim) it is stated: Sandra E. Horvath is a 57 Y female with family h/o Hashimoto's, sister has Sjogren's, taking mTX [sic], developed symmetric joint pains of b hands, knees and toes, associated with prolonged morning stiffness for many months.

   The words "many months" are not correct [.] [T]hey do not accurately describe the onset of my symptoms, and they are misleading with regard to my medical condition at that time. The symptoms pertaining to joint pain in my hands and knees along with fatigue came to my attention in the later September, 2012 timeframe. This is why I made the appointment with my primary care physician, Dr. Jing Qing Xu on October 3, 2012.

2. On page 51 of my medical records it states:
   Note: she has Sjogren's and could [sic] lupus, RA; but on page 41 the lab test for "Sjogren's –A AB Ser" is noted to be a negative value. Because of that the statement on page 51 that I have Sjogren's [sic] incorrect [.]

3. On page 107 of my medical records it states that I received a flu shot on August 7, 2012 and my symptoms began in October of 2012. This statement is not correct [.] I did receive a flu shot on September 20, 2012 and I have produced the consent form stating that to my doctors on several occasions. The symptoms began in late September as stated in #1 above.

Please make these corrections as soon as possible, and please ensure that they are [sic] accurately reflect what is written above.

On July 28, 2016, petitioner saw Dr. Lin. Med. recs. Ex. 86, at 173. Dr. Lin diagnosed petitioner with MCTD and said that her right hand was very suspicious for early presentation of scleroderma.[68] Id. at 177. She also had sicca. Id.

[68] Scleroderma is "chronic hardening and thickening of the skin, a finding in various different diseases. . . ." Dorland's at 1679.

On August 3, 2016, petitioner saw Dr. Richard A. Lau, a rheumatologist, for a second opinion. Id. at 196. Dr. Lau was at Kaiser Permanente Medical Group at Santa Clara, CA. Id. Petitioner reported that her symptoms began in 2012 possibly after a flu vaccination with arthralgia/myalgia diffusely throughout her body. Id. at 197. Dr. Lau's impression was "possible overlap syndrome, even MCTD as her RNP was positive (though no titer)" or could be "possible" undifferentiated connective tissue disease ("UCTD") as petitioner did not quite meet criteria for any specific CTD such as SSc or SLE with the exception of RA. Id. at 198. He wrote that petitioner had several concrete signs and symptoms suggestive of rheumatologic illness including arthralgia/myalgia (with synovitis on examination), Raynaud's phenomenon, heartburn, and scattered telangiectasia. She also had some other signs and symptoms that were more speculative such as tightening of the skin of her fingers with edematous changes which could be early signs of sclerodactyly and the recurrent oral ulcerations when she stopped taking MTX. Id.

On July 13, 2017, petitioner saw Dr. Lin. Med. recs. Ex. 91, at 1. Petitioner had been taking Mobic[69] for joint pains. Id. at 2. She writes under "allergies" that petitioner is allergic to flu vaccine. Id. at 3. She continues to diagnose her with MCTD and notes that petitioner had an abnormal nailfold capillary exam, a finding consistent in patients with Raynaud's phenomenon or scleroderma. Petitioner did not have significant synovitis. Id. at 6.

On August 3, 2017, petitioner saw Dr. Neelakshi Patel for a second opinion at Dr. Lin's request. (Actually, this was petitioner's third rheumatology evaluation since she saw Dr. Lau at Kaiser for a second rheumatology opinion). Med. recs. Ex. 102, at 2. The exhibit cover page and the medical record do not identify Dr. Patel as working at a hospital. The undersigned looked Dr. Patel up on the internet and found she is in private practice in San Jose and Los Gatos, CA.[70]

Petitioner gave Dr. Patel a history that she was in her usual state of health when she received a vaccine in 2012. Id. Two weeks later, she could not walk for two weeks. She started to have pain and stiffness in symmetrical joints of her hands, knees, and toes. Sometimes, her fingers were swollen. She found it hard to close her hand into a tight fist and had significant morning stiffness. She is on IV Actemra monthly. At present, she feels that one week prior to infusion, her symptoms return. Physicians at UCSF reviewed her file but did not see her. They thought she does not have MCTD. She wondered about her diagnosis and presented to Dr. Patel. Petitioner has dry eyes and mouth and occasional oral ulcers. She has ongoing fatigue which is worse the week before infusion. She was off work from 2002-2005 because of a back injury. Id. On physical examination, petitioner had unremarkable bilateral upper and lower extremities with

[69] Mobic is "trademark for a preparation of meloxicam." Dorland's at 1171. Meloxicam is "a nonsteroidal anti-inflammatory drug used in the treatment of osteoarthritis. . . ." Id. at 1126.

[70] Dr. Patel received her medical degree from Netaji Subhas Chandra Bose Medical College, Jabalpur, India, had an internship in internal medicine at the University of Massachusetts, had a fellowship in rheumatology at the University of California, Irvine, CA, and had a residency in internal medicine at Kaiser Permanente Medical Group. She is board-certified in rheumatology. She is affiliated with O'Connor Hospital, El Camino Hospital, and Good Samaritan Hospital, all in San Jose, CA. US NEWS & WORLD REPORT, https://health.usnews.com/doctors/neelakshi-patel-854330 (last visited September 24, 2018).

full range of motion and no deformities, synovitis, or pain with range of motion except for tender and mildly prominent PIP joints. Id. at 4. All of petitioner's fingers had mild, diffuse puffiness and slightly thickened skin, but still had elasticity. Petitioner had mild erythema on her checks and the bridge of her nose. She had a positive ANA of 1:320 in a homogeneous pattern and a positive RNP. Dr. Patel reviewed petitioner's capillaroscopy[71] photos which showed dilated capillary loops and tortuous loops. Dr. Patel noted that unfortunately she did not have access to all of petitioner's records. Id. Dr. Patel diagnosed petitioner with CTD, stating she certainly has Raynaud's phenomenon, mild early sclerodactyly, heart burn, malar erythema, and a positive ANA. Dr. Patel did not see active synovitis, but she also noted that petitioner was taking the drugs meloxicam, hydroxychloroquine, and Actemra, which likely were controlling her symptoms. Id. In addition, she might have a component of seronegative RA, such as inflammatory arthropathy. Id. at 4-5. Dr. Patel wrote that the only way to determine if petitioner has RA was for her to stop taking Actemra and see if she has an inflammatory flare. Id. at 5.

On November 15, 2017, petitioner returned to Dr. Lin. Med. recs. Ex. 113, at 5. Petitioner came to Dr. Lin to have nailfold capillary pictures taken. Id. at 6. She saw the rheumatologists Dr. Lau and Dr. Patel who concurred with the connective tissue disease diagnosis. But she needed the capillary pictures to show the UCSF rheumatologist who had never seen or examined her, but denied she has a connective tissue disease condition. Id. Dr. Lin diagnosed petitioner with MCTD and scheduled petitioner for a pulmonary function test and labs in three months. Id. at 9. If her arthritis symptoms became worse, she would consider doing hand x-rays to rule out erosions. Petitioner was to continue on Plaquenil and Actemra. Petitioner's friend took photos of her nailfolds and petitioner was going to mail them to Dr. Lin to put in her file. Id.

Other Material

On May 30 2013, petitioner's Dr. Tsai filled out a VAERS Report, stating petitioner received flu vaccine on August 17, 2012 (this is an incorrect date; the correct date is September 20, 2012), developed weakness several weeks later, and was diagnosed with MCTD several months later. Ex. 68, at 1.

Affidavits

On August 28, 2015, petitioner filed her first affidavit. Ex. 7. She said onset of pain and stiffness in her knees, hands, and lower back occurred within two weeks of her September 20, 2012 flu vaccination. Id. at ¶¶ 3 and 4. A few weeks later, she had extreme exhaustion. Id. at ¶¶ 5, 6. She retired on July 1, 2014 because of her symptoms. Id. at ¶ 22.

On August 28, 2015, petitioner filed her husband's affidavit, which was consistent with the information in his wife's affidavit. Ex. 8.

[71] Capillaroscopy is "diagnostic examination of the capillaries with the microscope." Dorland's at 283.

On July 21, 2017, petitioner filed her supplemental affidavit, discussing her course of disease and her nailfold capillary microscopy. Ex. 92.

On July 21, 2017, petitioner filed her husband's supplemental affidavit. Ex. 93.

On January 26, 2018, petitioner filed an affidavit concerning nailfold capillaroscopy images she provided to Dr. Lin. Ex. 114.

Medical Experts' CVs

Dr. S. Sohail Ahmed

Petitioner filed an updated CV for Dr. Ahmed on August 1, 2017. Ex. 95. Dr. Ahmed was an MD Anderson Cancer Center Research Fellow in immunology, researching the role of NK cells in murine melanoma in 1992. Id. at 4. He attended The University of Texas Medical School, Houston, TX, in 1993, receiving an M.D. in 1998. Id. at 5. During his time in medical school, he had an Alpha Omega Alpha research scholarship in 1996 to do HLA genotyping in rheumatoid arthritis. Id. at 4. That same year, he was a Sarnoff Cardiovascular Fellow to study the role of cellular actin and myosin in ventricular hypertrophy induced by aortic banding. Id.

Dr. Ahmed did an internal medicine residency at The University of Texas Medical School, from 1998-2000. Id. at 5. He was a Sarnoff Cardiovascular Scholar to study vascular disease development in scleroderma in 2000. Id. at 4. He was a Sarnoff Cardiovascular Scholar at The University of Texas Medical School, from 2000-2002. Id. at 5. During that time, he was a Wyeth–Ayers Rheumatology Fellow in 2001. Id. at 4. He also won a clinical investigator fellowship award from the Merck/American College of Rheumatology in 2002 and a Fellow Award from the Merck/American College of Rheumatology in 2002. Id. He was a clinical investigator at The University of Texas Medical School from 1998-2004. Id. at 5. During this time period, he was first author of a medical article relating that a certain subgroup of patients with RA had an increase in rheumatoid nodulosis that the drug MTX they were taking for RA had induced.[72] Dr. Ahmed was a rheumatology fellow at The University of Texas Medical School from 2002-2003. Id. at 4. In 2003, he was a top finalist in the Amgen Rheumatology Young Investigator proceeding. Id.

From 2003-2004, Dr. Ahmed was an Assistant Professor of Medicine in the Division of Rheumatology at The University of Texas Medical School. Id. From 2004-2006, he was an attending physician at the Veterans Administration Hospital in West Roxbury, MA, and at Boston University Medical Center. Id. at 3. From July 2004 to September 2006, he was Assistant Professor of Medicine at the Department of Medicine section of rheumatology at Boston University School of Medicine, becoming Clinical Assistant Professor of Medicine there from September 2006 – May 2007. Id. From 2006-2007, he received a grant from the

[72] S. Sohail Ahmed et al., The *HLA-DRB1*0401* Allele and the Development of Methotrexate-Induced Accelerated Rheumatoid Nodulosis: A Follow-Up Study of 79 Caucasian Patients with Rheumatoid Arthritis, 80 MEDICINE 4:271-78 (2001). Listed on Dr. Ahmed's updated CV. Ex. 95 at 6.

Scleroderma Foundation to be principal investigator of vascular disease and fibrosis in patients with systemic sclerosis. Id. at 4. From August 2007 to June 2008, Dr. Ahmed was a clinical associate in the Division of Rheumatology, Allergy, and Immunology at Harvard Medical School/Massachusetts General Hospital. Id. at 3.

From September 2006 to March 2008, Dr. Ahmed was a translational medicine expert at Novartis Pharma, Cambridge, MA. Id. He led the clinical development of novel compounds from Discovery (e.g., next generation follow-up to Gilenya) and mature compounds (e.g., Glivec) targeted for clinical profiling related to autoimmunity and inflammation. Dr. Ahmed managed a matrix-based team involving representatives from drug metabolism and pharmacokinetics, drug chemistry, research, toxicology, marketing, and clinical development to support design and implementation of proof-of-concept ("PoC") studies. He developed an approach incorporating modeling and simulations for the design of studies targeting immunosuppression and fibrotic pathways. He leveraged parallel collaborations with the Genomics Institute of the Novartis Research Foundation for the identification of human therapeutics (e.g., biologics) and their application to various autoimmune diseases. He was a clinical expert for in-licensing opportunities. Id.

From March 2008 to January 2011, Dr. Ahmed was head of the Clinical Science Unit, Translational Medicine, at Novartis Vaccines, Siena, Italy. Id. He directed an adjuvant safety initiative to enable an approach that was rational for preclinical studies using novel adjuvants such as toll-like receptor agonists to lessen safety risks in subsequent clinical trials. Id. Dr. Ahmed managed a team that was responsible for designing and implementing an exploratory trial of cell-mediated immunity from flu vaccination. He provided cross-functional support to the clinical development personnel in response to regulatory authorities on safety topics of autoimmune diseases associated with vaccination. He also led the design of clinical studies to reach PoC rapidly for Group A streptococcus and respiratory syncytial virus vaccines. Id.

From January 2011 to March 2015, Dr. Ahmed was Global Head of Clinical Sciences, at Novartis Vaccines, Siena, Italy. Id. at 2. He was Executive Manager. He was also chairman of a steering committee to develop antibody repertoire signatures that would predict natural, rapid recovery to guide future vaccine antigen discovery efforts or the design of clinical trials with patient groups most likely to respond to vaccine candidates in clinical development. He also led cross-functional teams working on staphylococcus aureus, influenza, or candida infections to ensure "seamless" application of this next-generation approach to vaccine development. Id. Dr. Ahmed managed the recruitment of applicants for World Health Organization-TDR Clinical and Development Fellowships to develop human resources promoting high-quality clinical research and development and enhancing capacity on diagnostics, drugs, and vaccines for infectious diseases that disproportionately affect poor and marginalized populations. Id. at 2-3. He led a cross-functional team to prioritize populations to be targeted with vaccines containing novel adjuvants such as TLR-agonists and pushed efforts to mitigate potential safety risks with a novel vaccine delivery platform of lipid nanoparticle self-amplifying RNA, e.g., anti-RNA antibodies and autoimmune disease risk. Id. at 3. Dr. Ahmed guided project leaders in principles of medicine and human infectious diseases to ensure preclinical studies aligned with subsequent

human target populations in vaccine clinical trials concerning clostridium difficile, nontypeable haemophilus influenza, and Escherichia coli. Id. He led the design of clinical trials and implemented exploratory studies to generate quick no/no go decisions that upper management made concerning subsequent product development with staphylococcus aureus and candida albicans. He managed a diverse matrix-based team involving clinical development, toxicology, technical development, vaccine chemistry, research/clinical serology, and regulation. Id.

From May to December 2015, he was global head of clinical sciences at GSK (GlaxoSmithKline) Vaccines, which acquired Novartis Vaccines in May 2015. Id. at 2. He was Executive Manager. He had the same responsibilities he had at Novartis Vaccines plus he managed an internal approach capitalizing on information technologies, e.g., health map which Harvard Medical School developed, in order to provide rapid surveillance for Neisseria meningitides disease activity and transmission in patients. Id. He led a two-tear global collaboration with 21 scientists and physicians from Novartis Vaccines, Novartis Pharma AG, Novartis Institutes of Biomedical Research, Atreca Inc., VisMederi Sri, Stanford University, Harvard Medical School, Dalhousie University, University of Siena, and the National Institute of Health and Welfare in Finland to: (1) reinforce the safety of emulsion adjuvants, e.g., MF59 and AS03; and (2) dissect the molecular pathway responsible for narcolepsy associated with the AS03-adjuvanted A (H_1N_1) pdm09 influenza vaccine. Id. Dr. Ahmed supervised a post-graduate course entitled "From Bench to Bedside: Principles of Vaccine Research & Development," covering principles of pre-clinical design and assessment of antigens, adjuvants, and formulation testing through the different phases of clinical evaluation, and elements of management and licensure. Id. He managed an internal cross-matrix team and external collaboration with a U.S. academic medical center to: (1) identify a correlate of protection for staphylococcus aureus by applying proteomic analysis to clinical sera from healthy subjects that are colonized compared to patients with infection; and (2) identify differences in antibody profiles from patients with various types of staphylococcus aureus infections, e.g., soft-tissue, joint, pulmonary, or blood infections, to enable selection of a patient subgroup most likely to support vaccine efficacy in clinical development trials. Id.

From April 2016 to the present, Dr. Ahmed has been at Translational Medicine, Roche Pharma AG, Basel, Switzerland, involved in immunology, inflammation, and infectious diseases, and leading cross-functional global teams to bring effective therapies for autoimmune diseases from the discovery phase to phase III clinical studies. Id.

Dr. Ahmed received an MBA at IE Business School, Madrid, Spain, in 2017. Id. at 5. He is licensed to practice medicine in Italy and the US. Id. at 1. He is board certified in internal medicine with a subspecialty in rheumatology. Id.

Dr. Ahmed belongs to the American Medical Association, the Stanley J. Sarnoff Cardiovascular Research Foundation, the American College of Physicians, the American College of Rheumatology, the Infectious Diseases Society of America, and the Beta Gamma Sigma Honor Society for Business. Id. at 4.

He has patents in sphingosine 1 phosphate receptor modulators and their use to treat muscle inflammation (WO2010010127A1), diagnostic and therapeutic methods for rheumatic heart disease based upon group A streptococcus markers (WO2011048561A1), and avoiding the risk of narcolepsy with influenza vaccines (WO2014180999A1). Id. at 5.

Dr. Ahmed's CV lists 11 articles, only two of which deal with rheumatic diseases and neither of those discusses clinical diagnosis. Id. at 5-6. His CV lists 18 reviews, letters, chapters, and editorials, only two of which deal with rheumatic diseases and neither of those discusses clinical diagnosis. Id. at 6-7.

During the last 12 years, Dr. Ahmed has been doing research and working for vaccine manufacturers. His clinical practice (as a clinical associate) ended in June 2008, 10 years ago.

Dr. Mehrdad Matloubian

Respondent filed the CV of Dr. Matloubian on June 23, 2016. Ex. B. Dr. Matloubian received his M.D. in 1996 from the University of California, Los Angeles. He also has a Ph.D. in virology. Id. at 1. He did an internship and residency in medicine at the University of California, San Francisco ("UCSF"),[73] from 1996-1998, and was a fellow in rheumatology at the same institution from 1998-2001, followed by a post-doctoral fellowship at the same institution from 1999-2004. Id. He has a medical license in California and is board certified in internal medicine with a subspecialty in rheumatology. Id. at 2. He has been at UCSF since 2001, holding positions as assistant adjunct professor, assistant professor in residence, associate professor in resident, and currently associate adjunct professor. Id. In 2001, he was awarded a Pfizer Postdoctoral Fellowship in Rheumatology/Immunology. In the same year, he received the American College of Rheumatology Distinguished Fellows Award. In 2003, he was awarded the Ephraim P. Engleman Award for Research in Rheumatology. Id. He states in his CV that, since July 2014, he has had a full-day clinic once a week and continues to attend one month on the inpatient rheumatology consult service. Id.

Dr. Matloubian is a member of the American College of Rheumatology, the Northern California chapter of the Arthritis Foundation, the American Association of Immunologists, and the American Society for Clinical Investigation. Id. at 2-3. He has written 33 articles, all of them on the immune response.

Medical Expert Reports filed before the hearing

On February 6, 2016, petitioner filed the expert report of Dr. Ahmed. Ex. 67, at 2.

Dr. Ahmed states in his expert report "the development of an autoantibody-mediated disease is the result of a complex interaction between genetic and environmental factors." Ex.

[73] UCSF is ranked in 2018-2019 as the seventh best hospital for adult rheumatology in the United States. Best Hospitals. Best Hospitals for Rheumatology, US NEWS & WORLD REPORT, https://health.usnews.com/best-hospitals/rankings/rheumatology (last visited September 24, 2018).

67, at 4. The most common skin involvement in MCTD is Raynaud's phenomenon. Id. Joint involvement and muscle pain are common in MCTD. A major cause of death in MCTD is pulmonary arterial hypertension ("PAH"). In answer to whether petitioner had signs and symptoms of MCTD before her September 20, 2012 flu vaccination, Dr. Ahmed says no. Id. at 5-6. She had pre-vaccination shoulder tendinitis in 2000 with x-ray showing calcifications of the supraspinatus muscle of the shoulder. Id. at 5. She had low back pain and right leg hypesthesia in 2001 related to a work injury when transferring a patient from a slideboard. Petitioner had asymmetric aching in the fingers and thumb of the right hand, a negative RF, a normal ESR, none of which suggests RA, but are more consistent with osteoarthritis. Id. Dr. Ahmed views the 2008 detection of ANA of 1:160 in a homogeneous pattern nonspecific which 20% of the normal population has. He thinks that her normal CPK muscle enzymes in August 9, 2000 and the nature of her musculoskeletal complaints make her having a myositis component of MCTD unlikely prior to her flu vaccination in 2012. Id. Her 2000 complaint of erythema in the face while having nausea and headaches was consistent with a vascular response, such as migraine. In 2014, petitioner was diagnosed with rosacea. Thus, Dr. Ahmed says the erythema of petitioner's face was not consistent with a malar rash, and she does not have the SLE of MCTD before flu vaccination in 2012. Id.

Dr. Ahmed says petitioner likely has high genetic susceptibility to MCTD because her mother has Hashimoto's[74] thyroid disease and her sister has Sjögren's syndrome ("SS") for which she takes methotrexate. Id. at 6. He states that since petitioner's immediate family members most likely carry genes that increased their susceptibility to autoimmune diseases associated with antibodies to the thyroid (Hashimoto's) or to glandular tissues (Sjögren's), petitioner's family history of autoimmune disease was a risk factor for her to develop autoimmune disease. Dr. Ahmed posits a sequence of events leading a genetically susceptible host presented with an antigen/peptid stimulus which her regulatory mechanisms failed to control, resulting in autoimmune disease, e.g., disease-specific autoantibodies such as anti-RNP. Id.

To answer the question whether petitioner developed MCTD after receiving flu vaccine in 2012, Dr. Ahmed comments that definitively diagnosing MCTD is often complicated since overlapping features of SLE, SSc, and inflammatory myopathy often occur associated with high titers of anti-RNP antibodies. He states a key feature to suspect MCTD is unexplained Raynaud's phenomenon. Diagnosing MCTD often takes years because of typical overlap features. After petitioner received flu vaccine on September 20, 2012, she saw Dr. Xu on October 3, 2012 with swelling in her hands for the first time. Blood tests showed antibodies to RNP with an index at 1.2 (Ex. 3, at 37-41), positive ANA tier of 1:320 (Ex. 3, at 45-46), which was greater than the prior titer of 1:160 four years earlier. From then on, petitioner's swelling and joint pain resembled RA (Ex. 3, at 98-101). Doctors put her on various disease-modifying anti-rheumatic drugs, including methotrexate, hydroxychloroquine, etanercept, abatacept, and

[74] Hashimoto disease is "a progressive type of autoimmune thyroiditis with lymphocytic infiltration of the gland and circulating antithyroid antibodies; patients have goiter and gradually develop hypothyroidism. It has a familial predisposition, usually affects women, and sometimes precedes the onset of Graves disease or is manifested after the major symptoms subside." Dorland's at 535. Graves disease can manifest as hyperthyroidism. Id. at 534.

tocilzumab. On May 13, 2013, she had elevated CRP and elevated complement levels, evidence for systemic inflammation, consistent with an evolving autoimmune disease (Ex. 3, at 86-89). On May 15, 2013, petitioner was noted to have skin thickening over her fingers (sclerodactyly), a feature of SS, which is another autoimmune disease (Ex. 3, at 98-101). Id.

Dr. Ahmed opines that the two-week interval between petitioner's 2012 flu vaccination, detection of disease-specific autoantibodies for MCTD, and increasing ANA titer fall within a plausible window for linking flu vaccine to the dysregulation of petitioner's immune response. Id. at 7. Petitioner's gradual progression of clinical symptoms (eight months after vaccination, systemic inflammation detected in lab tests and thickening of skin of her fingers; 18 months later, Raynaud's phenomenon diagnosed) is typical for MCTD. Dr. Ahmed concludes that the presence of autoantibodies to RNP and Raynaud's phenomenon occurring after flu vaccination on September 20, 2012 suggests a causal relationship. Id. In the alternative, the flu vaccination of September 20, 2012 may have caused significant aggravation of an underlying autoimmune process that was asymptomatic, transforming it into a clinically apparent disease. Petitioner's initial positive ANA detected on March 5, 2008 may have been due to her October 7, 1999 flu vaccination priming her (Ex. 14, at 20; Ex. 16, at 1). Priming involves generating immune memory in a vaccinee. Thus, petitioner's initial immune response to flu vaccination on October 7, 1999 started the process of asymptomatic autoimmunity and the next flu vaccination administered October 14, 2009 further boosted it. The flu vaccination she received on September 20, 2012 could have also boosted the immune response, transforming the underlying autoimmunity into an autoimmune disease, i.e., MCTD. Ex. 67, at 7.

Dr. Ahmed says that vaccines can cause autoimmune diseases even if epidemiologic studies do not confirm that because of the small number of cases, unlike the considerable number of cases of GBS (500) among 45 million people who received swine flu vaccine in 1976. Id. at 8. He says "rare adverse events still occur in genetically susceptible subjects…." Id. Dr. Ahmed states that molecular mimicry has been demonstrated specifically for MCTD in reaction to various viruses: HIV, Epstein-Barr virus, and human influenza B virus dealing with systemic sclerosis. Id. at 9.

On June 23, 2016, respondent filed the expert report of Dr. Mehrdad Matloubian. Ex. A. Dr. Matloubian doubts that petitioner has MCTD and suspects that her musculoskeletal pain is related to her chronic pain syndrome and osteoarthritis, and therefore unrelated to her flu vaccinations. Id. at 5-6. He says MCTD is considered an overlap syndrome because it has features of other better-defined autoimmune diseases, such as SLE, SS, and polymyositis. Id. at 6. The symptoms may occur over time, thus making diagnosis at the outset of the disease challenging. He states a major characteristic of patients whom doctors eventually diagnose with MCTD is the presence of Raynaud's phenomenon in association with high-titer speckled ANA with fine specificity for U1 RNP. The remaining criteria are clinical signs showing inflammatory disease, e.g., myositis, acrosclerosis, synovitis, and swollen hands. Id.

Dr. Matloubian states that when Dr. Lin diagnosed petitioner with MCTD on October 31, 2012, she based her diagnosis on petitioner's non-specific joint complaints without any clinical

sign of synovitis and primarily because petitioner had a positive anti-RNP. Dr. Matloubian regards petitioner's positive anti-RNP as a false positive result which does not support a diagnosis of MCTD. On October 15, 2012, petitioner's serologic tests showed a low to moderate ANA titer of 1:320 with a homogeneous pattern (Ex. 3, at 45-46). This result is consistent with petitioner's previous ANA test done in 2008, which was positive at 1:160 with a homogeneous pattern (Ex. 14, at 20). A homogeneous pattern as petitioner had corresponds to anti-dsDNA, nucleosomes, and histones, usually seen in SLE, drug-induced lupus, and autoimmune thyroid disease. Ex. A, at 6. In contrast, when someone has antibodies to U1-RNP, such as someone with MCTD, the staining pattern is speckled, not homogeneous. Id. at 7. Dr. Matloubian's opinion is that petitioner's homogeneous ANA result on two separate tests performed at two different laboratories suggests the anti-RNP result was most likely a false positive. Id.

Dr. Matloubian has other issues with this positive anti-RNP test result. Firstly, the assay showed a low positive anti-RNP at 1.2 with the cutoff for this assay being less than 1 and the highest value being 8. Dr. Matloubian does not know how the tech person reached a value of 1.2 and how this relates to an ANA titer of 1:320, but in light of the moderate ANA titer and the homogeneous pattern, petitioner's 1.2 value does not seem to qualify for the high titer ANA (>1:10,000) with speckled pattern that is a mandatory diagnostic criterion for MCTD. Secondly, in addition to testing for anti-RNP, petitioner was tested for anti-Sm+RNP, and the result was negative (Ex. 3, at 41). Since the same antigens are used to test for RNP as for Sm+RNP, Dr. Matloubian expected both test results to be positive. Bio-Rad Laboratories, which manufactures this assay, has a statement that if someone has a positive RNP test, but a negative SmRNP and Sm test, this decreased the probability of connective tissue disease. Ex. 7, at 7. Bio-Rad Laboratories' Interpretation Guide also indicates that this result can be seen in 2.3% of normal blood donors.[75] Id.

Dr. Matloubian concludes that if petitioner had a truly positive anti-RNP associated with MCTD, she should have had high-titer speckled ANA, positive anti-RNP (AI >8) and three positive autoantibodies; all of the MCTD patients were positive for RNP and SM+RNP. Dr. Matloubian ascribes petitioner's false positive anti-RNP result to the type of bead-based multiplex assay that Bio-Rad Laboratories used to determine autoantibodies. Id. He states many experts have raised concerns about the sensitivity and specificity of such assays. False positives are not uncommon and Dr. Matloubian thinks petitioner is an example of a false positive. She initially tested low positive for anti-cardiolipin IgM and IgG antibodies, but testing several months later resulted in normal results (Ex. 3, at 63, 82). He strongly believes based on his own experience with patients whose lab results are contradictory that petitioner's anti-RNP test result was a false positive. Id.

[75] On August 1, 2017, respondent filed as exhibit E the Bio-Rad Laboratories BioPlex 2200 Interpretation Guide: SmRNP vs Sm & RNP. If someone tests negative for Sm, positive for RNP, and negative for SmRNP, the interpretation guide states: "If low titer without other associated antibodies, decreased probability of connective tissue disease; retest patient every 6-12 months to monitor titer. Potential predictive antibody for early stage SLE." The prevalence of this test result of negative Sm, positive RNP, and negative SmRNP is 2.3% in normal blood donors, and 4.1% in rheumatology patients. Id.

Dr. Matloubian describes petitioner's treating rheumatologist Dr. Lin's charting of petitioner's clinical symptoms of MCTD as "not ideal." Id. at 8. He noted that Dr. Lin did not correct her initial incorrect diagnoses in subsequent records and her records have many internal inconsistencies. Id. Dr. Matloubian describes as "clear" was Dr. Lin's not observing petitioner having hand or joint swelling or clear synovitis when petitioner first came to her on October 31, 2012. During the next three years, Dr. Lin documented only one possible swelling in a PIP joint (Ex. 3, at 124) which apparently resolved. He states Dr. Lin never documented diffuse hand swelling in petitioner, even though diffuse hand swelling is often seen in early MCTD. Dr. Lin thought petitioner might have sclerodactyly. Id. Being certain of the presence of synovitis is more difficult in patients, such as petitioner, who are overweight. Id. Petitioner's BMI on May 17, 2013 was 30 (Ex. 3, at 99). Dr. Matloubian would have used an MRI to determine if petitioner had synovitis, but Dr. Lin did not perform any imaging studies of petitioner, such as x-rays of her hand and knees or an MRI of her hands to detect inflammation or other causes of joint pain, such as osteoarthritis. Id. Dr. Matloubian thinks Dr. Lin diagnosed MCTD solely based on the results of the RNP test without any clinical findings to support the diagnosis and then over time looked for signs and symptoms to justify her diagnosis. Dr. Matloubian noted that 75 percent of patients with MCTD have lung involvement including pulmonary hypertension, but Dr. Lin did not order a high-resolution CT or echocardiogram to screen petitioner for this possibility. In addition, Dr. Lin did not note administering a PPD[76] test, which is a requirement before beginning a patient on anti-TNF therapy such as Enbrel. Id.

Dr. Matloubian says patients with MCTD generally have Raynaud's disease as an early symptom. Id. But the earliest notation Dr. Lin made of petitioner having Raynaud's phenomenon is November 19, 2014, a year after Dr. Lin diagnosed petitioner with MCTD. Id. at 9. Petitioner does not mention in her affidavit dated August 2015 that Raynaud's phenomenon was part of her symptoms. Dr. Lin again diagnosed petitioner with Raynaud's phenomenon on January 5, 2016 and prescribed topical medication (Ex. 20, at 1-5). Dr. Matloubian states that it would be quite unusual for Raynaud's phenomenon to be a late manifestation of MCTD. Dr. Matloubian thinks that petitioner's moderately positive ANA with a homogeneous pattern is more consistent with autoimmune thyroid disease than MCTD. Id. That petitioner's sister has Sjögren's disease, which is autoimmune, increases the likelihood that petitioner would have a positive ANA. Id.

Dr. Matloubian thinks petitioner's true diagnosis is chronic pain syndrome and osteoarthritis, both of which predate her flu vaccination in September 2012. Id. at 10. As for Dr. Ahmed's opinion, Dr. Matloubian takes issue with Dr. Ahmed's reliance on the theory of molecular mimicry because the presence of linear sequence homology does not necessarily translate to immunogenicity. Id. at 11. Proteins consist of linear sequences of amino acids, but fold into complex three-dimensional structures. Dr. Ahmed's diagram in Exhibit 25 is too simplistic and does not convey that a similar linear sequence of amino acids in one protein may be hidden within its three-dimensional structure and not accessible to antibodies. Id. Thus sequence homology is insufficient evidence for molecular mimicry. Id. at 12. Concerning the

[76] PPD is "purified protein derivative (tuberculin). . . ." Dorland's at 1506. Tuberculin is "used in skin tests for tuberculosis" and is also "a commonly used antigen in laboratory immunology." Id. at 1979.

theory that if a vaccine can cause a disease, so can the infection that the vaccine was created to prevent cause the same disease, Dr. Matloubian did medical article research, but could not find any medical articles linking flu virus infection with MCTD. Id. at 12-13. He concludes that since the flu virus shares genetic similarity with components of flu vaccine but is not associated with MCTD, it is highly unlikely that a mechanism such as molecular mimicry causes MCTD due to flu vaccine. Id. at 13.

Dr. Matloubian is unimpressed with the two-fold change in ANA titer petitioner had from 1:160 in 2008 to 1:320 in 2012 because the change has unclear clinical significance. Id. He takes issue with Dr. Ahmed's opinion that petitioner's 1999 and 2009 flu vaccinations primed her ANA, which the 2012 flu vaccination then boosted so that petitioner developed autoimmune disease. Id. at 14. Dr. Matloubian questions why, if the 1999 flu vaccination primed petitioner, the 2009 flu vaccination did not boost her to have clinical autoimmune disease, instead of just being another priming vaccination. To Dr. Matloubian, it seems as if Dr. Ahmed were interpreting events to fit his thesis and not considering other interpretations. Id. Dr. Matloubian does accept the prime and boost theory as applied to an acute infection or a vaccination when someone's immune system is exposed briefly to an antigen, but it does not make sense in the context of an autoimmune response for which self-antigen persists. He gives an example of a memory response proceeding to a reaction against poison ivy or poison oak. When someone is exposed to poison ivy, he may have no symptoms but is immunized and generates memory T-cells to the plant's antigens. When the person has a subsequent exposure, he develops a severe and rapid response within a couple of days due to expansion of poison ivy specific memory T-cells and localization to exposed areas. This response also subsides because the antigen is not persistent. Thus, the poison ivy specific memory T-cells are dormant and do not cause any symptoms. Id.

Dr. Matloubian says a similar process occurs after flu immunization, i.e., generation of memory T-cells to the vaccine component. These memory T-cells are inactive unless they encounter their specific antigen through exposure to flu virus or re-immunization with the same seasonal flu vaccine. If Dr. Ahmed's opinion that prior flu vaccinations generate memory T-cells that are cross-reactive for self-antigens is correct, Dr. Matloubian says he would not expect these cells to be dormant and inactive waiting for another flu vaccination since their putative self-antigens are always around and constantly stimulating them. In addition, they would not need a boost from another flu vaccination since their antigen is a self-antigen and always present. To Dr. Matloubian, Dr. Ahmed's explanation does not make biologic sense. Id.

Dr. Matloubian further discounts Dr. Ahmed's opinion that petitioner has a genetic predisposition and thus was susceptible to developing an autoimmune disease because immediate family members have autoimmune diseases. He states that multiple studies in medical literature show that patients with autoimmune diseases receive vaccinations, including against flu, without exacerbation of their disease or developing a new one. Id.

Dr. Matloubian concludes his report by stating petitioner's tests do not support a diagnosis of MCTD because MCTD necessitates a high-titer ANA with a speckled pattern. Id. at

15. Petitioner on two occasions had two different laboratories conclude she had a relatively low-titer ANA with a homogeneous pattern, inconsistent with a diagnosis of MCTD. Moreover, petitioner's marginally positive anti-RNP was most likely a false positive. Dr. Matloubian opines petitioner suffers from chronic pain syndrome and osteoarthritis, both of which pre-existed her September 2012 flu vaccination. Id.

On June 28, 2016, petitioner filed Dr. Ahmed's response to Dr. Matloubian. Ex. 70. Dr. Ahmed states that a low-titer positive RNP suggests a decreased probability of connective tissue disorder, but does not exclude the diagnosis of MCTD. Id. at 2. Guidelines for diagnosing MCTD capture most, but not all, MCTD patients. Id. Dr. Ahmed states that natural flu infection but not flu vaccine have been observed to exacerbate RA and SLE. Id. at 4. He explains this discrepancy as due to degree, duration, and dispersion of inflammation in the context of a systemic infection which is greater than the controlled immune stimulation involved in vaccination. Id. Dr. Ahmed states, "In my opinion, it is possible that influenza vaccination triggered MCTD" in petitioner. Id. at 5.

On July 11, 2016, respondent filed Dr. Matloubian's response to Dr. Ahmed. Ex. C. He reiterates that he thinks Dr. Lin's assessment of petitioner suffers from confirmation bias, i.e., her subsequent records presume her initial diagnosis of MCTD was correct without considering other possible causes of petitioner's symptoms. Id. at 2. He is suspicious of Dr. Lin's physical examinations of petitioner. Id. He states that Dr. Ahmed's interpretation of petitioner's numbness in the bottom of her feet as indicative of Raynaud's phenomenon is absolutely incorrect. Id. at 3. Dr. Matloubian denies that petitioner was ever diagnosed with scleroderma and did not have documented laboratory features of scleroderma which most commonly affects the skin and lungs. Id. He reiterates that petitioner's ANA was low specificity and can be seen in autoimmune thyroid disease, with which petitioner was diagnosed. Id. at 6. He notes that the ANA titer does not correlate with disease activity. Id. Dr. Matloubian also notes that the Bio-Rad laboratory insert states that 2.3 percent of blood donors have borderline positive anti-RNP and negative everything else. Id.

Dr. Matloubian asked his rheumatology colleagues at UCSF, including the Chief of the UCSF Rheumatology Clinic and the director of the UCSF Scleroderma Center, how they would interpret petitioner's test results and they unanimously said that the anti-RNP was a false positive and they would repeat the test with a different type of assay. Id. at 7. They also said petitioner did not have MCTD and they had great doubt that she had any rheumatologic disease. He also asked a rheumatology colleague who has practiced at Kaiser in the bay area about petitioner's serologies and he replied that the subserologies were done by automated testing and the so-called BioPlex testing and unfortunately automated testing can give non-specific results. Id.

Dr. Matloubian agrees with Dr. Ahmed that natural infections, such as flu virus, lead to a much stronger immune response that immunization with inactivated flu vaccine. Id. at 11. Thus, it would be highly unlikely for a vaccine, which induces a much weaker immune response than a natural infection, to lead to autoimmune disease when the natural infection with the flu virus itself is not associated with that autoimmune disease. Id. Dr. Matloubian concludes with the

statement:

> As a practicing rheumatologist at a major academic referral center, neither I nor any of my colleagues would have diagnosed the petitioner as having MCTD or any other rheumatologic autoimmune disease based on the provided serological testing for autoantibodies. Her anti-RNP test result, the sole basis of the diagnosis of MCTD made by Dr. Lin, was most likely a false positive since it was discordant with the remainder of her test results. It is my strong opinion that the petitioner did not develop MCTD or any other rheumatic autoimmune disease as the result of receiving the influenza vaccine.

Id. at 12.

On August 19, 2016, petitioner filed Dr. Ahmed's response to Dr. Matloubian. Ex. 87. Dr. Ahmed states that patients with autoimmune disease do not always fulfill the standard criteria. Id. at 6. Most of the standard criteria were designed for the purpose of following and classifying patients in clinical studies. Moreover, the association of anti-RNP antibodies with MCTD does not occur in up to 5 percent of patients with MCTD. Therefore, it is not always present in MCTD. If petitioner did not have anti-RNP antibodies, that would not exclude her from the diagnosis of MCTD in light of her clinical signs after flu vaccination. Id. Dr. Ahmed explains petitioner's ANA homogeneous pattern as due either to the 5 percent of MCTD patients who do not have RNP antibodies, or the laboratory detecting the ANA pattern used a different technology and thus reflected a different pattern at initial dilutions. Id. at 8. Dr. Ahmed states that antibodies can fluctuate during a stage of a disease and a low positive does not mean a false positive. He says the manufacturer Bio-Rad states that a low-titer positive RNP suggests a decreased probability of connective disorder. This does not mean a low-titer positive RNP excludes the diagnosis of MCTD since five percent of patients with MCTD do not have anti-RNP antibodies. Id.

Dr. Ahmed states that molecular mimicry is not speculative and is proven for streptococcus and rheumatic fever. Id. at 9. The theory is also accepted to explain GBS following the 1976 swine flu vaccine campaign. Id.

On May 2, 2017, respondent filed the second supplemental report of Dr. Matloubian responding to the additional medical records (Ex. 86) and Dr. Ahmed's supplemental report (Ex. 87). Ex. D. He states that he highly doubts the diagnosis of MCTD and recommended petitioner seek a second opinion from a doctor with an academic rheumatology practice, such as Stanford or UCSF. Id. at 3. However, petitioner obtained a second opinion from Dr. Lau, who is another rheumatologist at Kaiser Permanente, just as Dr. Lin is. Id. Dr. Lau "speculated" petitioner could have MCTD or UCTD. Id.

Dr. Matloubian notes that petitioner had one positive anti-RNP result while another RNP antigen test (anti-RNP/Smith) was negative. This is highly unusual. Id. at 3. That makes two

discrepancies in her autoantibody testing, which makes these tests results inconsistent with a diagnosis of MCTD. Id. at 3-4. The consultant rheumatologist Dr. Lau appeared to be unaware that petitioner had a history of rosacea when he diagnosed her with CTD. Id. at 4. What is more, Dr. Lau attributed petitioner's skin problem as telangiectasia due to connective tissue diseases. Id. Petitioner's GERD predates her flu vaccination on September 20, 2012. Id. Dr. Matloubian disagrees that the pictures of petitioner's fingers reflect active Raynaud's phenomenon. Id. at 5. Petitioner's main complaints are musculoskeletal pain, but she does not have elevated muscle enzymes, which rules out inflammatory myopathy (usually associated with MCTD and other connective tissue diseases). Two of petitioner's rheumatologists, Dr. Lau and Dr. Lin, performed physical examinations of petitioner within one week and came to different conclusions as to what they saw. Determining a diagnosis of joint inflammation in an overweight patient such as petitioner makes the doctors' conflicting diagnoses suspect. Id. This is why Dr. Matloubian relies on objective studies as MRIs to detect joint inflammation. Dr. Lau appeared unaware that petitioner's oral ulcers when she was not taking MTX were due to herpes simplex virus and treated with acyclovir. Id. Dr. Matloubian states that some of the therapies petitioner received, e.g., Enbrel, Orencia, and Actemra, could have led to her developing further autoantibodies. Id. at 6. He states if he were petitioner's treating rheumatologist, he would repeat autoimmune tests using an ELISA[77] assay, discontinue her immunosuppressive medications, do MRI imaging of her hands while she was off medications to evaluate her for joint inflammation, and treat her with gabapentin or pregabalin for her chronic pain syndrome. Id.

Medical Articles

Petitioner's Medical Articles

Petitioner filed as Exhibit 22 Dr. Ahmed's reference 7 in his first expert report (Ex. 67), a medical article by Hidetoshi Kaneoka et al., Molecular Genetic Analysis of HLA-DR and HLA-DQ Genes Among Anti-U1-70-kd Autoantibody Positive Connective Tissue Disease Patients, 35 ARTHRITIS & RHEUMATISM 1:83-94 (1992). The authors state that patients with systemic rheumatic disease such as SLE and MCTD frequently have autoantibodies against U small nuclear ribonucleoproteins ("[U]snRNP"). Id. at 83. They discuss different research finding an association of autoantibodies reactive with U1 RNP (U1-70-kd[78]) and different types of HLA, i.e., HLA-DR4 and HLA-DR2.[79] Id. at 83, 90. They state:

[77] ELISA is "[*e*nzyme-*l*inked *i*mmunosorbent *a*ssay] any enzyme immunoassay utilizing an enzyme-labeled immunoreactant (antigen or antibody) and an immunosorbent (antigen or antibody bound to a solid support). A variety of methods (e.g., competitive binding between the labeled reactant and unlabeled unknown, or a sandwich technique in which the unknown binds both the immunosorbent and labeled antibody) may be used to measure the unknown concentration." Dorland's at 605.

[78] Kd stands for "kilodalton." A kilodalton is "a unit of mass, being one thousand (10^3) daltons." Dorland's at 986. A dalton is "an arbitrary unit of mass, being 1/12 the mass of the nuclide of carbon-12, equivalent to 1.657×10^{-24} g. Called also *atomic mass unit*." Id. at 470.

[79] HLA are "human leukocyte antigens." Dorland's at 864. HLA complex is "histocompatibility antigens governed by genes of the HLA complex (the human major histocompatibility complex), a region on the short arm of chromosome 6 containing several genetic loci, each having multiple alleles. Loci are designated by letters; the classical loci are HLA-A, -B, -C, -E, -F, -G, -DP, -DQ, and -DR (there are at least three subloci in the D region). Alleles at each locus are designated by numbers. HLA-A1, provisional designations being indicated by "w" (for

> Both genetic and nongenetic factors may contribute to the production of anti-U1-70-kd autoantibodies. While HLA-DR genes are associated with the presence of anti-U1-70-kd autoantibodies, it is clear that the majority of individuals possessing these genes do not have anti-U1-70-kd autoantibodies, not do they develop CTD. This could be explained by interactive effects between and among nongenetic factors and multiple genes that contribute to autoantibody production.

Id. at 91. The authors posit, "The finding of the association of specific HLA genes with the presence of autoantibodies reactive with the U1-70-kd polypeptide could be compatible with an immune response gene-regulated and antigen-driven immune response [citations omitted]." Id.

No doctor ever tested petitioner for HLAs of any type.

Petitioner filed as Exhibit 26 Dr. Ahmed's reference 1 in his first expert report (Ex. 67), a medical article by Gordon C. Sharp et al., Mixed Connective Tissue Disease—An Apparently Distinct Rheumatic Disease Syndrome Associated with a Specific Antibody to an Extractable Nuclear Antigen, 52 AM J MED 2:148-59 (1972). The authors state that they observed in a clinic over eight years a spectrum of patients with rheumatic disease whose serum contained a high titer of ANA which persisted through periods of active disease and clinical remission. Id. at 148-49. The authors comment that common to all patients with MCTD are high titers of speckled pattern on fluorescent ANA testing. Id. at 156.

Petitioner filed as Exhibit 27 Dr. Ahmed's reference 2 in his first expert report (Ex. 67), a chapter by Robert Bennett, Scleroderma, inflammatory myopathies, and overlap syndromes, 1381-99, in KELLEY'S TEXTBOOK OF RHEUMATOLOGY (8th ed. 2008), but what she actually filed was Robert Bennett, Overlap Syndromes, 1431-51, chapter 86 in KELLEY'S TEXTBOOK OF RHEUMATOLOGY (Gary S. Firestein et al., 2012). On page 1440, Bennett states, "The first clue to diagnosing MCTD is usually a positive ANA with a high-titer speckled pattern. The titer is often greater than 1:1000 and sometimes greater than 1:10,000. … [P]atients destined to follow a course most consistent with MCTD have sera with predominant U1-RNP reactivity." On page 1441, Bennett states, "Early in the course of the disease most patients complain of easy fatigability, poorly defined myalgias, arthralgias, and Raynaud's phenomenon . . . ." Petitioner did not have a high-titer positive ANA and high-titer serum antibodies to RNP. She did not have Raynaud's phenomenon until two years after her initial diagnosis.

Petitioner filed as Exhibit 28 Dr. Ahmed's reference 3 in his first expert report (Ex. 67), an article by Melissa R. Arbuckle et al., Development of Autoantibodies before the Clinical

"workshop"), e.g., HLA-DRw10. The A, B, C, and DR antigens are defined and typed by serologic reactions. The D antigens are defined and typed by one-way mixed lymphocyte culture (MLC) using panels of HLA-D-homozygous typing cells. The SB (for "secondary B cell") antigens are defined and typed by primed lymphocyte typing." Id. at 105.

Onset of Systemic Lupus Erythematosus, 349 NEJM 16:1526-33 (2003). Arbuckle explains that SLE is virtually always accompanied by the production of autoantibodies. Id. at 1527. Since autoantibodies contribute directly to the pathologic changes of SLE, Arbuckle states their development must coincide with or precede the clinical symptoms of SLE. Arbuckle evaluated serum samples of 130 persons in the US Armed Forces who received a diagnosis of SLE. Id. In 101 patients, there was a nine-year interval between the detection of ANA in their sera and their first clinical sign of SLE. Id. at 1529. The proportion of patients with SLE who had anti-Sm or anti-RNP increased dramatically the year before their SLE diagnosis. Id. at 1530. These findings reflect the close temporal relationship between development of these autoantibodies and clinical disease. Id. Arbuckle concludes that some autoantibodies (ANA, anti-Ro, anti-La, and antiphospholipid antibodies) usually preceded the onset of SLE by many years. Id. at 1531. Anti-Sm and Anti-RNP antibodies typically appeared only months before diagnosis during the time when characteristic clinical manifestations appeared. Id.

ANA are relatively common in normal persons who never have clinical symptoms of rheumatic disease. However, anti-RNP antibodies are very rare in normal persons. Id. Arbuckle states that the data of sera of a substantial proportion of patients (69 percent) were censored because autoantibodies were present in the first available serum sample, which was obtained a mean of four years before diagnosis. Id. at 1532. But she says if she could have seen serum samples obtained before the development of autoantibodies for all patients, her estimates of the mean time from autoantibody development to clinical diagnosis would have been longer. "Consequently, this study provides a lower-boundary estimate of the time before the diagnosis at which particular autoantibodies develop." Id.

Arbuckle concludes based on the serological and clinical findings along with prior studies that there are at least three phases in the development of SLE autoantibodies: (1) the normal phase in which the person is asymptomatic with no SLE autoantibodies (only 32 patients or 25 percent of the 130 patients who developed SLE were in this first, normal phase); (2) the benign autoimmunity phase, in which a laboratory finding of ANA, anti-Ro. anti-La, or antiphospholipid antibodies were present, but without immediate clinical manifestations of SLE; and (3) the pathogenic autoimmunity phase, in which the more ominous autoantibodies—anti-dsDNA, anti-Sm, and anti-NRP antibodies—were present as was the onset of signs and symptoms leading to a clinical presentation and diagnosis of SLE. Id. Arbuckle states data showing increased concentrations of autoantibodies before diagnosis and progressive accrual of autoantibody specificities at the epitope level also support this concept of a crescendo of autoimmunity culminating in clinical disease, a process usually underway for many years before diagnosis. Id.

Petitioner filed as Exhibit 29 Dr. Ahmed's reference 4 in his first expert report (Ex. 67), an article by Robert M. Bennett & Dennis J. O'Connell, Mixed Connective Tissue Disease: A Clinicopathologic Study of 20 Cases, 10 SEMIN ARTHRITIS RHEUM 1:25-51 (1980). The authors give the origin of the diagnostic entity of MCTD:

> In 1972, Sharp and his coworkers described an overlap syndrome of SLE, generalized scleroderma, and polymyositis, which they

> considered a "distinct rheumatic disease syndrome," giving it the name Mixed Connective Tissue Disease (MCTD). The unifying feature of this concept was the presence of antibodies to a saline extractable nuclear antigen (ENA) that was RNAase sensitive. Subsequent work by Mattioli and Reichlin has resolved ENA into two distinct moieties: soluble ribonucleoprotein (RNP) and a glycoprotein termed "Sm' antigen. RNAase-sensitive ENA is synonymous with RNP; RNP antibodies are a sine qua non for the diagnosis of MCTD . . . [footnotes omitted].

Id. at 25. All the patients included in the authors' study had a high-titer speckled pattern antinuclear factor. Id. at 42. The RNP antibody titer did not correlate with disease activity. Id.

Petitioner filed as Exhibit 30 Dr. Ahmed's reference 5 in his first expert report (Ex. 67), a review by Sevdalina N. Lambova & Stefka J. Kuzmanova, Raynaud's Phenomenon in Common Rheumatic Diseases, 48 FOLIA MEDICA (PLOVDIV) 22-28 (3 & 4 2006). The authors state that Raynaud's phenomenon occurs about 85 percent in MCTD and often as one of the initial symptoms. Id. at 26. Some authors (Alarcon-Segovia and Villareal, Kasukawa, et al. and Sharp) define Raynaud's phenomenon as one of the criteria of MCTD. Id. They state anti-U1-RNP antibodies appear to be a specific immune marker for MCTD. Id.

Petitioner filed as Exhibit 31 Dr. Ahmed's reference 6 in his first expert report (Ex. 67), an article by Siri Tennebø Flam et al., The HLA profiles of mixed connective tissue disease differ distinctly from the profiles of clinically related connective tissue diseases, 54 RHEUMATOLOGY 528-35 (2015). The authors state that MCTD is identifiable by high-titer serum antibodies to U1-70 kDa RNP and a complex phenotype that encompasses Raynaud's phenomenon, puffy hands, arthritis, pleuritis, pericarditis, myositis, esophageal dysmotility and/or lung fibrosis. Id. at 528. They state the etiology of MCTD is unclear but may involve chronic immune activation after exposure to environmental risk factors in those with a predisposing genetic background. Id. at 529. Similar to other CTDs, genetic factors within the HLA complex appear important. Id. The authors discovered that the HLA associations observed in MCTD differ from the HLA associations seen in SLE and SSc. Id. Across different populations, MCTD appeared to be associated with HLA-DR4 allelic variants, whereas SLE and PM/DM were primarily associated with HLA-DR3 and SSc with DR5. Id. The authors' HLA analysis confirmed that MCTD is an immune-mediated disease distinct from SLE, SSc, and PM/DM. Id. at 532.

Petitioner mistakenly filed as a second Exhibit 31 Dr. Ahmed's reference 7 (which petitioner mistakenly marked as reference 6) and then filed the same article as Exhibit 32 Dr. Ahmed's reference 7 (but still marked as reference 6) in his first expert report (Ex. 67), an article by Hidetoshi Kaneoka et al., Molecular Genetic Analysis of HLA-DR and HLA-DQ Genes Among Anti-U1-70-kd Autoantibody Positive Connective Tissue Disease Patients, 35 ARTHRITIS RHEUM 1:83-94 (1992). The authors state that autoantibodies against U small nuclear ribonucleoproteins ("[U]snRNP") are frequently present in the sera of patients with systemic

rheumatic diseases, e.g., lupus and MCTD, and serve as useful markers for diagnosis. Id. at 83. MCTD is associated with HLA-Dq1 as well as HLA-DQw3. Id. The authors find interesting the association of anti-U1-70-kd autoantibody positive CTD with more than one HLA allele. Id. at 90. The authors posit that finding an association of specific HLA genes with the presence of autoantibodies reactive with the U1-70-kd polypeptide could be compatible with a gene-regulated and antigen-driven immune response. Id. at 91. The authors recognize that both genetic and nongenetic factors may contribute to the production of anti-U1-70-kd autoantibodies, and that while HLA-DR genes are associated with the presence of anti-U1-70-kd autoantibodies, it is clear that the majority of individuals possessing these genes do not have anti-U1-70-kd autoantibodies or develop CTD. This could be explained by interactive effects between and among nongenetic factors and multiple genes that contribute to autoantibody production. Id.

Petitioner filed as Exhibit 33 Dr. Ahmed's reference 8 in his first expert report (Ex. 67), a short analytical review by Robert W. Hoffman & Marcos E. Maldonado, Immune pathogenesis of Mixed Connective Tissue Disease: A short analytical review, 128 CLIN IMMUNOL 1:8-17 (2008). The authors state MCTD is a systemic autoimmune disease which the presence of autoantibodies and T-cells reactive with U1-RNP polypeptides of the spliceosome complex including their associated uridine-rich (U) small nuclear RNAs. Id. at 8. Sharp et al. in 1972 described MCTD patients as a novel group based on the presence of high levels of antibodies against an extractable nuclear antigen (ENA) that was RNase- and trypsin-sensitive. Id. Sharp et al. showed that ENA contained both the ribonuclease (RNase)- and trypsin-sensitive RNP antigen associated with MCTD. Id. at 9.

The authors state there are four published classification criteria for MCTD. Id. The authors state the primary clinical features of MCTD are Raynaud's phenomenon, swollen fingers or diffusely swollen hands, arthralgia, with or without associated arthritis, esophageal reflux or esophageal dysmotility, acrosclerosis (i.e., sclerodactyly), mild myositis, and pulmonary involvement of a variety of forms. Id. Characteristic immunologic findings in MCTD are a high-titer fluorescent antinuclear antibody (FANA) with a speckled pattern and the presence of antibodies to RNP at moderate to high level in the serum. Id. Patients with MCTD have an increased frequency of HLA-DR4 compared to healthy controls. Id. The initial emergence of anti-RNP antibodies has a strong association with clinical disease. Id. at 10. The authors state that independent observations over the past decade converge with the view that both the innate and adaptive immune systems play central roles in the development of many systemic autoimmune diseases including MCTD. Id. at 11. Citing Sharp and his colleagues, the authors state that anti-RNP antibodies are required for the diagnosis of MCTD and to meet any of the four classification criteria developed for MCTD. Id. at 12. They state that anti-RNP antibody in MCTD can constitute up to one-third of total serum immunoglobulin in some patients. Id.

Moreover, the authors state a hallmark of MCTD is hypergammaglobulinema. Id. They write the anti-RNP and anti-U1-RNA antibodies display immunoglobulin class switching to immunoglobulin G (IgG). Id. Petitioner was never diagnosed with hypergammaglobulinema and testing of her IgG levels always showed a normal result.

Citing the Arbuckle[80] study of banked sera of military personnel who developed lupus-like disease, the authors of this article recount Arbuckle's discovery that military personnel developed onset of clinical disease within one year after testing of their sera showed they had anti-RNP antibodies without clinical disease. Id. In addition the authors in this article state that the presence of IgG anti-U1-RNA antibodies is a well-documented feature of MCTD. Id.

Petitioner filed as Exhibit 34 Dr. Ahmed's reference 9 to his first expert report (Ex. 67), an article by Susan Cappelli et al., "To Be or Not To Be," Ten Years After: Evidence for Mixed Connective Tissue Disease as a Distinct Entity, 41 SEMIN ARTHRITIS RHEUM 4:589-98 (2012). The authors state the initial clinical presentation of MCTD usually includes Raynaud's phenomenon, swollen puffy hands, and polyarthritis or polyarthralgias. Id. at 590. High-titer anti-U1 snRNP antibodies are a serologic marker for MCTD and an association of HLA-DR4 haplotype has been observed with both anti-U1 snRNP and with MCTD per se. Id. The authors studied 161 patients diagnosed with MCTD. Id. At the first visit of these 161 patients to a doctor for diagnosis, 93.2 percent had Raynaud's phenomenon, 96.9 percent had ANA, and 100 percent had anti-RNP. Id. at 592.

Petitioner filed as Exhibit 35 Dr. Ahmed's reference 11 to his first expert report (Ex. 67), an article by Sumit Sen et al., Cutaneous Manifestations of Mixed Connective Tissue Disease: Study from a Tertiary Care Hospital in Eastern India, 59 INDIAN J DERMATOL 1:35-40 (2014). The authors state MCTD is associated with the presence of antibody against a specific uridine-rich U1RNP. Id. at 36. They classified 23 patients with MCTD when they were serologically positive for U1RNP at a titer of 1:1600 or higher, with the presence of at least three clinical features, e.g., edema of the hands, synovitis, myositis, Raynaud's phenomenon, and acrosclerosis. Id. Most of those in the study group tested positive for ANA and the pattern was solely speckled. Id. at 39.

Petitioner filed as Exhibit 45 Dr. Ahmed's reference 20 to his first expert report (Ex. 67), an editorial by David S. Pisetsky, Antinuclear antibodies in healthy people: the tip of autoimmunity's iceberg? 13 ARTHRITIS RES THER 2:109-10 (2011). The author states that 20 percent or more of otherwise healthy people can express an ANA. Id. at 109.

Petitioner filed as Exhibit 57 Dr. Ahmed's reference 32 to his first expert report (Ex. 67), an article by himself and others, Assessing the Safety of Adjuvanted Vaccines, 3 SCI TRANSL MED 93:93rv2:1-10 (2011). Ahmed, citing a study, notes that flu infection but not flu vaccine exacerbated preexisting autoimmune disease. Id. at 2. He states that vaccine antigens are screened for molecular mimicry to exclude autoantigens in vaccine intended for humans. Id. The adjuvants used in vaccines for humans differ from strong adjuvants, such as complete Freund's adjuvant, used in animal studies which deliberately break immunological tolerance in the animals to study animal models of autoimmune disease. Id. Ahmed states:

> Human autoimmune diseases are diverse and complex, and the

[80] Melissa R. Arbuckle et al., Development of autoantibodies before the clinical onset of systemic lupus erythematosus, 349 NEJM 1499-1500 (2003). Ex. 28.

> nature of the trigger cannot be simplified to the point that one "test" can be reliably expected to predict disease induction. Evaluating the effects of a vaccine or adjuvant on one or two disease models within this category would provide no information about the effects on other diseases within the category. Difficulties and limitations with these tests include the differences between animal disease models and real human disease as well as fundamental genetic and physiological differences between humans and commonly used laboratory animals. … In addition, factors that initiate disease in animal models might not necessarily be relevant to human disease development. … Both the incomplete correlation with human disease and the divergent mechanisms of disease initiation limit the relevance of even the "best" animal models to specific human diseases.

Id. at 4.

Dr. Ahmed states that a major hurdle facing development of predictive biomarkers for vaccine-related autoimmune disease is the absence of predictive markers for spontaneous human autoimmune disease. Id. Dr. Ahmed analyzes three parts of this hurdle. Id. at 5. Firstly, scientists do not know how identified biomarkers would behave in the context of immunization. Id. Secondly, biomarker data are inconsistent and unreliable when the source of them is doctors and their vaccinated patients. Thirdly, scientists would need to collect and store blood samples from tens of thousands of subjects to attain adequate statistical power to evaluate biomarkers of rare adverse events that occur after a delayed period of time post-vaccination such as autoimmune disease or autoimmune-related symptoms. Id.

Dr. Ahmed says:

> With the introduction of any vaccine there is the risk for coincidental association with naturally occurring autoimmune disease. That is, in any population, there is a background rate of these events that occur despite vaccination and a concomitant risk of such event occurring at the same time as the vaccine, by chance alone. These 'temporal' associations can confound the interpretation of vaccine safety

Id.

Dr. Ahmed notes that "the possibility that autoimmune diseases may begin months or years before clinical diagnosis poses logistical challenges, emphasizing the importance of discovering biomarkers predictive for autoimmune disease." Id. at 6. Dr. Ahmed lists a number of factors that must be considered when evaluating whether or not a vaccine adverse event occurred: environment, diet, age-related changes in the immune system, and conditions

associated with triggering autoimmune disease in susceptible subjects, such as pregnancy or exposure to natural infections. Id. at 8. Dr. Ahmed thinks following vaccinated subjects to detect autoimmune adverse events should extend out to six months. Id. He notes that older epidemiologic studies followed 18,000 recipients of flu vaccine for 16 to 18 years without detecting an increase in allergic and autoimmune diseases. Id.

Petitioner filed as Exhibit 79 Dr. Ahmed's reference 9 of his supplemental expert report (Ex. 70), a medical article by Hans H. Guldner et al., Human Anti-P68 Autoantibodies Recognize a Common Epitope of U1 RNA Containing Small Nuclear Ribonucleoprotein and Influenza B Virus, 171 J EXPERIMENTAL MED 3:819-29 (1990). The authors used small nuclear ribonucleoprotein particles ("U1snRNP") as a model system. Anti-U1snRNP autoantibodies are characteristic for certain inflammatory rheumatic diseases, and a 68-kD protein (p68) of the U1snRNP particle is a major antigenic target. Id. at 819. Thirty-five percent of 103 anti-p68 autoimmune sera recognized a particular autoreactive region in amino acid position 234-253, which the authors term domain A. Id. at 820. They demonstrate that a subset of human anti-p68/domain A autoantibodies react with a p68 epitope present on the matrix protein M1 of human influenza B viruses, and that autoimmune sera recognized this shared epitope. Id. The authors took these sera from patients with MCTD and SLE. Id. The influenza strains were B/Beijing/1/87[81] and A/Singapore/6/86 (H_1N_1). Id.

The authors conclude that a subset of human anti-p68 autoantibodies recognize an epitope shared by the p68 autoantigen and the influenza B virus M1 matrix protein. Id. at 824. They posit that autoimmune sera of antibodies reactive with a shared epitope may represent molecular mimicry and implicate influenza B viruses as triggers for the development of autoantibodies to p68. Id. at 825. The authors identified a sequence motif of five amino acids as an autoepitope that a subset of anti-p68 autoantibodies from (U1) RNP-positive patients' sera recognized. Id.

They note that influenza viruses may contribute to autoimmune disease because they interact with lymphocytes, which may lead to partial breakdown of self-tolerance, and they can cause polyclonal B cell activation, considered important for autoantibody formation. In addition, flu viruses impair the function of phagocytes, which may lead to delayed clearance of self-antigens, and p68 as an RNA-binding protein may interact with flu virus RNA and be secreted in virus-encapsulated form, rendering extracellular p68 as a possible target for B cells. Lastly, a high percentage of flu virus-infected patients develop autoantibodies. Id. at 825-26. In addition to possibly initiating autoimmunity by molecular mimicry, influenza B might promote such an antigen-driven process by releasing snRNP as a result of virus-induced cell lysis. Id. at 826. The authors state that "not all individuals infected with influenza B would be expected to develop anti-p68 autoantibodies." Id. Other predisposing factors such as genetic predisposition, immune deficiency, and hormonal, environmental, and other influences would be necessary. Id.

[81] B/Beijing/1/87 is of the Victoria lineage. Phylogenetic tree for the HA gene and trend of strains in different countries, RESEARCH GATE, https://www.researchgate.net/figure/Phylogenetic-tree-for-the-HA-gene-and-trend-of-strains-in-different-countries-A_fig2_295084193 (last visited October 22, 2018).

The 2012-2013 influenza vaccine that petitioner received on September 20, 2012 contained A/California/7/2009-like virus (pH_1N_1), A/Victoria/361/2011-like virus (H_3N_2), and B/Wisconsin/1/2010-like virus (Yamagata lineage). Update: Influenza Activity – United States, 2011-12 Season and Composition of the 2012-2013 Influenza Vaccine, 61 MORBIDITY AND MORTALITY WEEKLY REPORT (MMWR) 22:414-20, Centers for Disease Control and Prevention (June 8, 2012).[82] It is unclear to the undersigned if Guldner's research in 1990 using B/Beijing/1/87 (Victoria lineage) influenza virus on sera as he and his co-authors described in Exhibit 79 is relevant to petitioner who received B/Wisconsin/1/2010 flu vaccine in 2012, 23 years after B/Beijing/1/87/flu virus was circulating, although the authors state they found the ERKRR motif also within the M1 matrix protein of B/Lee/40 and B/Singapore/222/79 flu viruses. Ex. 79, at 822.

Significantly, Guldner and his co-authors did not find the cross-reaction of human anti-ERKRR autoantibodies with influenza B M1 protein in anti-p68 sera from patients with various rheumatic diseases and high titers of autoantibodies to other antigens (e.g., Sm, Ro, La centromere, topoisomerase I, PM-Scl, histones, dsDNA, fibrillarin, and Jo-1) or in >50 healthy individuals whom they tested. Id. at 824.

Petitioner would not presumably fit in either of the non-responding groups because she does not have high titers of autoantibodies to these multiple antigens or even high-titer ANA or high-titer anti-RNP, but she claims she has a CTD and therefore cannot be considered healthy. Moreover, petitioner did not have an autoimmune reaction to her October 7, 1999 flu vaccination, which raises the question of how receipt of B virus vaccine would have promoted the development of human anti-ERKRR autoantibodies with influenza B M1 protein if she had anti-p68 sera at all. Her reaction to the 1999 flu vaccine was left supraspinatus tendinitis. She probably had SIRVA because she had left arm pain and difficulty raising her left arm. SIRVA is the result of improper vaccination rather than a reaction to vaccine components.

Petitioner had no reaction whatsoever to her October 14, 2009 flu vaccination, which again exposed her to B virus vaccine. Yet, Dr. Ahmed testified that her flu vaccinations in both 1999 and 2009 created a booster or priming effect so that when she received on September 20, 2012 B/Wisconsin/1/2010-like virus of Yamagata lineage, the vaccine caused her an autoimmune rheumatic disease. It is a non sequitur to link a 1999 vaccination which mechanically-induced pain with a 2009 vaccination to which petitioner had no reaction at all to a 2012 vaccination after which rheumatic disease was finally diagnosed and claim, as Dr. Ahmed does, that the rheumatic illness was due to the repeated exposure of petitioner to the flu B strain virus in a killed virus vaccine. Petitioner's history of SIRVA (1999), no reaction (2009), and putative rheumatic illness (2012) over a span of 13 years does not support an opinion that boosting, priming, or rechallenge is present in this case.

Petitioner filed as Exhibit 72 (but marked as Exhibit 1) Dr. Ahmed's reference 2 of his supplemental expert report (Ex. 70), an article by Minoru Satoh et al., Clinical interpretation of antinuclear antibody tests in systemic rheumatic diseases, 19 MOD RHEUMATOL 3:219-28 (2009).

[82] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6122a4.htm (last visited October 17, 2018).

The authors note that while information of ANA testing includes staining pattern (speckled, homogeneous, or peripheral), it is relatively subjective and varies depending on the laboratory or individual reading the results. Id. at 220. They state that the classic feature of MCTD is associated with very high titers of anti-U1RNP antibodies. Id. at 221. They note that higher titers of ANA do not always mean that the patient's disease is more severe or active. However, specificity of autoantibodies is a factor correlating strongly with titers of ANA. Autoantibodies such as anti-U1RNP and centromere may show titers of 1:10,240 or even higher. Individuals with high titers of these antibodies may be classified as having undifferentiated connective tissue disease (UCTD) or Raynaud's disease, and may not require any medical treatment. Id.

Petitioner filed as Exhibit 75 Dr. Ahmed's reference 5 of his supplemental expert report (Ex. 70), an article by Jonathan Graf, Antinuclear Antibodies, in PRIMER ON THE RHEUMATIC DISEASES (12th ed. 2001), consisting of two pages. On the first page, Dr. Graf writes under "Speckled pattern (ENA or acid extractable nuclear antigens)," under MCTD, the anti U1-RNP is nearly 100% sensitive.

Petitioner filed as Exhibit 89 attached to Dr. Ahmed's responsive report (Ex. 87), a one-page ARUP Consult entitled Mixed Connective Tissue Disease – MCTD.[83] Under serological criteria for diagnosis, the report lists anti-RNP ≥1:1,600 plus three or more of these clinical signs: edema of hands; synovitis; myositis; Raynaud syndrome; and acrosclerosis. Petitioner would not have satisfied these criteria on October 31, 2012 when she saw Dr. Lin because petitioner's anti-RNP was 1.2, not ≥1:1,600, and she did not have any of those clinical signs. Dr. Lin described puffy fingers, not edema of the hands, and myalgia or muscle aching, not myositis which is inflammation of the muscles. In addition, the ARUP Consult requires under the category of laboratory testing an abnormal CRP (which petitioner did not have) and abnormal connective tissue antibody testing, including an ANA showing a centromere pattern usually of >1:1,000 (petitioner's centromere testing was negative) and a speckled pattern (petitioner's ANA pattern was homogeneous, not speckled). Other ARUP tests show hypergammaglobulinemia, but petitioner's IgG was normal.

Respondent's Medical Articles

Respondent filed as Tab 1, Dr. Matloubian's reference 1 of his first expert report (Ex. A), an article by Robert M. Bennett, Definition and diagnosis of mixed connective tissue disease, UPTODATE.[84] Bennett states:

> A key feature in suspecting a diagnosis of MCTD is the presence of unexplained Raynaud phenomenon. If systemic sclerosis can be ruled out and the patient has a speckled-pattern antinuclear antibody (ANA) usually in high titer, further immunological

[83] ARUP CONSULT. THE PHYSICIAN'S GUIDE TO LAB TEST SELECTION AND INTERPRETATION, https://arupconsult.com/content/mixed-connective-tissue-disease (last visited October 15, 2018).
[84] UPTODATE, http://www.uptodate.com/contents/anti-u1-rnp-antibodies-in-mixed-connective-tissue-disease (last visited September 11, 2018).

> testing is warranted. The finding of anti-RNP antibodies provides further important, but not conclusive, evidence for a diagnosis of MCTD.

Id. at 1-2.

Respondent filed as Ex. A, Tab 2, Dr. Matloubian's reference 2 of his first expert report (Ex. A), an article by Oscar-Danilo Ortega-Hernandez & Yehuda Shoenfeld, Mixed connective tissue disease: An overview of clinical manifestations, diagnosis and treatment, 26 BEST PRAC & RES CLIN RHEUM 61-72 (2012). The authors state MCTD was first described in 1972 as an illness with mixed features of SLE, "SSc", polymyositis/dermatomyositis ("PM/DM"), and "RA" along with the presence of high-titer anti-U1 small nuclear ("sn") anti-RNP antibodies. Id. at 61. The most common clinical manifestations of MCTD are Raynaud's phenomenon, arthralgias, swollen hands, fingers with a sausage-like appearance, and muscle weakness. Id. at 62. These symptoms appear in 90 percent of patients and usually develop insidiously. Id. The authors state that anti-U1-RNP antibodies are the hallmark of MCTD. Id. at 64. They state that diagnosis of MCTD is not often easy due to the wide spectrum of clinical findings. Id. at 65.

In Table 1, the authors list different criteria from various authors for diagnosing MCTD. Id. at 66. In the Donato Alarcón-Segovia publication,[85] the anti-RNP titer needs to be greater than 1:1.600. Id. In the Gordon C. Sharp article,[86] the anti-U1-RNP titer needs to be at least 1:1000. Id. In the Marcel-Francis Kahn publication,[87] the presence of anti-RNP must be at a titer of $\leq$1:2000 with a speckled pattern of ANA. Id. Ortega-Hernandez and Shoenfeld conclude that MCTD has a wide spectrum of clinical manifestations and that some patients may have mild, self-limited disease. Id. at 69.

Respondent filed as Ex. A, Tab 3, Dr. Matloubian's reference 3 of his first expert report (Ex. A), an article by Chiara Tani et al., The diagnosis and classification of mixed connective tissue disease, 48-49 J AUTOIMMUN 46-49 (2014). The authors state that the presence of antibodies against the U1snRNP autoantigen is considered the serologic hallmark of MCTD. Id. at 46. They state: "For classification purposes, the presence of anti-U1RNP autoantibodies is mandatory. . . ." Id. at 48.

Respondent filed as Ex. A, Tab 4, Dr. Matloubian's reference 4 of his first expert report (Ex. A), an article by Robert M. Bennett, Clinical manifestations of mixed connective tissue disease, UPTODATE.[88] Dr. Bennett's first sentence under "Introduction" is: "Mixed connective tissue disease (MCTD) is defined as a generalized connective tissue disorder characterized by the

[85] Classification and diagnostic criteria for mixed connective tissue disease, MIXED CONNECTIVE TISSUE DISEASE AND ANTINUCLEAR ANTIBODIES 33-40 (Reiji Kasukawa and Gordon C. Sharp eds., 1987).
[86] Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA), 52 AMER J MED 148-69 (1972).
[87] Syndrome de Sharp in LES MALADIES SYSTEMIQUES 545-56 (Marcel-Francis Kahn et al. eds., 3d ed. 1991).
[88] UPTODATE, http://www.uptodate.com/contents/clinical-manifestations-of-mixed-connective-tissue-disease?topicKey=RHEUM%2F7546&elapsedTimeMs=2&source-search_result&selectedTitle=1-84&usage_type=default&display_rank=1 (last visited October 15, 2018).

presence of **high titer anti-U1 ribonucleoprotein (RNP) antibodies** in combination with clinical features commonly seen in systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polymyositis (PM) [emphasis added]." Id. at 1. He states, "The most common skin change is the Raynaud phenomenon, which usually presents early in the course of the disease." Id. at 2. Furthermore, "The Raynaud phenomenon is a typical early feature of MCTD. . . ." Id. at 5. Dr. Bennett also states a high-titer speckled ANA is "highly suggestive of a MCTD diagnosis" and "its fine specificity of anti-U1 RNP is the emblematic serological finding in MCTD." Id. at 6. Other serologic abnormalities include hypergammaglobulinemia. Id. at 7.

Respondent filed as Ex. A, Tab 5, Dr. Matloubian's reference 5 of his first expert report (Ex. A), an article by Dr. Donald B. Bloch, Patient information: Antinuclear antibodies (ANA) (Beyond the Basics), UPTODATE.[89] Antibodies directed against one's own body in autoimmune diseases are called autoantibodies. Id. at 1. The level to which a patient's blood sample can be diluted and still have recognizable staining of the sample is known as the ANA titer. Id. Dr. Bloch states, "It is difficult to standardize the ANA test between laboratories." Id. He also states, "A positive test for antinuclear antibodies (ANA) does not, by itself, indicate the presence of an autoimmune disease." Id. at 3.

Respondent filed as Ex. A, Tab 8, Dr. Matloubian's reference 8 of his first expert report (Ex. A), an article by Katrin Op De Beéck et al., Antinuclear antibody detection by automated multiplex immunoassay in untreated patients at the time of diagnosis, 12 AUTOIMMUN REV 137-43 (2012). ANA determined by BioPlex 2200 in patients with various connective tissue diseases are depicted in Table 1. One hundred percent of MCTD patients had ANA reactive against RNP and smRNP antigens. Id. at 140. (Petitioner's testing of RNP was positive but of smRNP was negative.) The authors state, "Patients with systemic rheumatic diseases have circulating autoantibodies to various nuclear target antigens." Id. They state the likelihood for disease increases with increasing antibody concentration. Id. at 142.

Respondent filed as Ex. A, Tab 9, Dr. Matloubian's reference 9 of his first expert report (Ex. A), an article by Kevin G. Moder et al., Measurements of Antinuclear Antibodies by Multiplex Immunoassay: A Prospective, Multicenter Clinical Evaluation, 34 J RHEUMATOL 5:978-86 (2007). The authors state that in patients with MCTD among other rheumatic diseases, "there were high rates of agreement for the various disease-specific autoantibodies overall and among positive sera." Id. at 981.

Respondent filed as Ex. A, Tab 14, Dr. Matloubian's reference 14 of his first expert report (Ex. A), chapter 24 by Sangeeta D. Sule & Fredrick M. Wigley, Raynaud Phenomenon, CURRENT DIAGNOSIS & TREATMENT: RHEUMATOLOGY (John B. Imboden et al. eds., 3d ed. 2013). The authors state that "Anti-dsDNA, anti-Ro/SS-A, anti-La/SS-B, anti-Sm, and anti-RNP antibodies are most characteristic of SLE…, Sjögren syndrome…, or mixed connective tissue disease." Id. at 3.

[89] UPTODATE, http://www.uptodate.com/contents/antinuclear-antibodies-ana-beyond-the-basics?topicKey=PI%2F574&elapsedTimeMs=3&view=print&displayedView=full# (last visited October 15, 2018).

Respondent filed as Ex. A, Tab 24, Dr. Matloubian's reference 24 of his first expert report (Ex. A), an article by Elizabeth Benito-Garcia et al., Guidelines for Immunologic Laboratory Testing in the Rheumatic Diseases: Anti-Sm and Anti-RNP Antibody Tests, 51 ARTHRITIS RHEUM 6:1030-44 (2004). The authors state the antigen to which anti-Sm antibodies bind consists of a series of proteins complexed with small nuclear RNAs: U1, U2, U4-6, and U5. Id. at 1030. These complexes of nuclear proteins and RNAs are called snRNPs. Id. Both the Sm and RNP antigens are located on the U1snRNP, which is why anti-RNP is sometimes referred to as anti-U1 RNP and anti-U1 snRNP antibodies. Id. "High titers of anti-RNP are a requisite for the diagnosis of MCTD [references omitted]." Id.

TESTIMONY

Dr. Syed Sohail Ahmed testified first for petitioner. Tr. at 12. At the time of the hearing in 2017, Dr. Ahmed had been working in the vaccine industry for eight years. Id. at 13. He has done research in animal studies and humans. He was in patient care previous to that for about 17 years at The University of Texas Health Science Center at Houston, the Boston University School of Medicine, and the Harvard Medical School - Massachusetts General Hospital where he had a scleroderma clinic. Dr. Ahmed was also an academic investigator about 20 years, working on Phases I and II-related clinical studies. Id. His internship at the University of Texas was a combination of general medicine, rheumatology, and rheumatology research. Id. at 14. He said he had learned the limitations of research on animals as applied to humans because we are all genetically very different. Id. at 15. He said "humans are very different from animals." Id.

Dr. Ahmed has experience making vaccines at Novartis Vaccines and GlaxoSmithKline. Id. Dr. Ahmed said someone needs to have a genetic susceptibility to autoimmune disease in order to have a reaction to a vaccine. Id. at 25. Each person has a signature called a human leukocyte antigen or HLA. Certain autoimmune diseases are linked to certain HLA signatures. Id. He stated mixed connective tissue disease is very rare. Id. at 27. There is an unsaid agreement that a lot of autoimmune diseases start as infections and then go on to become autoimmune diseases. Id. at 30. An example is reactive arthritis for which scientists have isolated the organism that causes it. Id.

Dr. Ahmed currently works at Hoffmann-La Roche in Basel, Switzerland, leading the translational medicine efforts to develop drugs that block autoimmune disease. Id. at 33. He was board-certified in general medicine in 2003 and in rheumatology in 2004. Id. at 34. Those are 10-year certifications. He did not renew them because he moved to Italy, but he recertified in Europe in 2013, and maintains an active medical license in Massachusetts. Id. He also has a license to practice medicine in Italy. Id. at 35. Dr. Ahmed works with others at La Roche to identify the best diseases to target for drugs. Id. at 36. He is responsible for overseeing the design of human clinical trials, selecting patient groups, and monitoring adverse events. Id. He also has to interface with regulatory agencies. Id. at 37. He has many contacts with rheumatologists at tertiary care centers in the US and is a contributing author to Noel Rose's The Autoimmune Diseases[90] in writing the chapter on vaccines and autoimmunity. Id. at 38-39. Dr.

[90] Noel R. Rose & Ian R. Mackay eds., The Autoimmune Diseases (5th ed. 2014). Dr Ahmed co-authored with Dr.

Ahmed also contributed to the textbook Plotkin's Vaccines.[91]

Dr. Ahmed justified diagnosing a patient with a rheumatic disease even if the patient did not fulfill enough criteria to merit the diagnosis because "you have to start somewhere with patients." Id. at 44. Dr. Ahmed said that applying to a human what he learned using animal models, e.g., if an animal model for lupus has a defective mechanism, would not work because the distribution of immune receptors in animals is not the same as in humans and the genetics in animals is not the same as in humans. Id. at 44-45.

He thinks MCTD should be called a variant of an overlap syndrome. Id. MCTD has some features of lupus, myositis (a muscle inflammatory disease), and scleroderma. Id. MCTD is associated with an antibody called U1-RNP antibody. Id. at 46. Doctors diagnose people with MCTD who have high titer, anti-RNP antibodies and three out of five other clinical criteria. Id. at 46-47. With petitioner, the question is whether or not her anti-RNP antibody titer is high enough to merit a diagnosis of MCTD. Id. at 47.

The other issue pertaining to petitioner's test result of anti-RNP antibody is whether it was a false positive. Petitioner's treating doctors mention areas of swelling that could be consistent with synovitis and these are clinical criteria that are important for diagnosing MCTD. He thinks petitioner's anti-RNP antibody "could have been higher" to merit the diagnosis of MCTD. But if the patient fulfills the clinical criteria, he would not dismiss the patient's having MCTD even if the anti-RNP antibody titer were negative. Id. Dr. Ahmed said that with autoimmune disease, the scenario is not that the patient is not normal one day and has high-titer antibodies the next day. Id. at 48. Instead, autoimmune disease is progressive and takes time. Id.

Dr. Ahmed referred to the Arbuckle article (Ex. 28) involving the sera from military recruits. Id. at 49. Some of the military recruits developed lupus. Arbuckle went back to their initial blood samples, before these recruits had the clinical signs of lupus, and tested the sera for

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Paul-Henri Lambert chapter 20, "Autoimmune Diseases: The Role for Vaccines." On page 279, Dr. Ahmed and Dr. Lambert state "natural infection, unlike vaccination, is a *more likely and proven risk factor* for triggering ('flare') and augmenting severity of autoimmune diseases [emphasis in original]." They compared patients with autoimmune diseases who had viral and bacterial infections with patients with autoimmune diseases who were vaccinated and, in every study, those with autoimmune diseases who had the infection were worse off compared to the vaccinated autoimmune group. Id. at 279-80. Influenza and other acute respiratory infections were also commonly associated with an increased frequency of relapses in autoimmune patients. This risk was markedly reduced in patients who received the seasonal flu vaccine. Id. at 280.

[91] Stanley A. Plotkin et al., eds., Plotkin's Vaccines (7th ed. 2018). Dr. Ahmed is the lead author with two co-authors Dr. Ronald W. Ellis and Dr. Rino Rappuoli of chapter 66, "Technologies for Making New Vaccines." On page 1283, Dr. Ahmed and his co-authors define inactivated vaccine as one containing "an immunogen that cannot replicate in the host as the disease-causing microbe has been killed with chemicals, heat, or radiation." "[T]his type of vaccine usually requires multiple doses, often followed by booster doses, for attaining long-term protective immunity." Id. at 1290. The 6th ed. of Plotkin's Vaccines (2013) has the same chapter with Dr. Ronald W. Ellis as the lead author with two co-authors Dr. Rino Rappuoli and Dr. Sohail Ahmed, starting on page 1182. The 5th ed. of Plotkin's Vaccines (2008) has the same chapter but with just Dr. Ronald W. Ellis as the sole author, starting on page 1335.

antibodies, such as ANA. Arbuckle found that these recruits had ANA antibodies before their autoimmune disease clinically developed. Dr. Ahmed said that ANA can be seen in 10 to 20 percent of the normal population as well. Id.

Dr. Ahmed said we all kill ourselves every day if our cells recognize a virus or a cancer cell. Id. at 49-50. But we shut off this daily autoimmune reaction, except for those people who develop autoimmune disease. Id. at 50. They fail to regulate the mechanism and proceed to have autoimmune disease with a specific disease marker. Id.

Dr. Ahmed said molecular mimicry depends on how the protein and the epitope[92] fold. Id. at 52. He referred to the Guldner article (Ex. 79) which shows mimicry between influenza B strain and a portion of the antigen that MCTD recognizes. Id. at 54. The undersigned asked Dr. Ahmed if he was a lumper or a splitter. Id. at 55. He answered that earlier in his training, he was a splitter although his mentors were lumpers. Id. at 56. Dr. Ahmed said that as he learned more after gaining experience, he became more of a lumper. Id.

Dr. Ahmed said the reason people receive flu vaccines yearly is that the protein used changes frequently. Id. at 60. He said, "The immune system wanes with time and then responds." Id. Dr. Ahmed said the Arbuckle paper (Ex. 28) clearly shows there is a time frame for the development of autoimmune disease. Id. at 62. If priming and boosting occur close enough in time, it could tip the person to autoimmune disease. Id. at 63. Dr. Ahmed said he would not necessarily call petitioner's flu vaccination in 1999 and flu vaccination in 2009, 10 years later, a prime/boost. Id. at 64. In petitioner's case, the presence of ANA before 2012, but the development of inflammation in the blood, elevated C-reactive protein, after her receipt of flu vaccine suggests generalized inflammation that was not present before. Id. at 66. Dr. Ahmed said MCTD typically occurs in women 20 to 30 years old, but petitioner was 57 when she had it. Id.

Dr. Ahmed said that having a low-titer RNP antibody is not useless for diagnosing MCTD. Id. at 67. To Dr. Ahmed, what is important is that a positive RNP antibody is the sine qua non for diagnosing MCTD. Id. at 68. Petitioner also developed Raynaud's phenomenon, puffiness of her fingers, thickening of her skin, and a distribution that could be consistent with synovitis. That is enough for Dr. Ahmed to believe that flu vaccine caused it, particularly since petitioner was susceptible to having an autoimmune disease due to her mother's having Hashimoto's and her sister having Sjögren's. Autoimmune diseases tend to run in families. Id. Dr. Ahmed testified that petitioner's medical records before September 20, 2012 do not indicate clinically or through blood work that she had inflammation in her body or anything that would suggest to him that she had MCTD before her September 20, 2012 flu vaccination. Id. at 71. Dr. Ahmed mentioned that this case was the first case in which he has testified in court as an expert. Id.

Dr. Ahmed defined MCTD as a constellation of a blood value result of anti-RNP antibodies at a high titer and of clinical findings of swelling or puffiness of the fingers, synovitis,

[92] Epitope means "antigenic determinant." Dorland's at 637.

sclerodactyly or acrosclerosis (thickening of the skin), Raynaud's phenomenon, and inflammation of the muscle (myositis). Id. at 89. Dr. Ahmed said the diagnosis depends on which criteria one wants to follow. Alarcön-Segovia sometimes substitutes muscle pain (myalgia) for muscle inflammation (myositis). Id.

Dr. Ahmed said that not all MCTD patients have anti-RNP antibodies. Id. at 90. However, it is a very important antibody because people with high-titer RNP antibodies have earlier Raynaud's phenomenon. Id. Dr. Ahmed said that in his clinical experience in Texas and Boston, he has seen at least 1,000 scleroderma patients and at least 100 MCTD patients. Id. at 95. At his last appointment, he opened a scleroderma center for Massachusetts General Hospital. Id. at 96.

Dr. Ahmed is confident petitioner has MCTD because she does not fulfill criteria for any other disease and she has the symptoms that make up the constellation that is called MCTD. Id. at 111. His opinion is that flu vaccine caused it because women who have MCTD have it earlier in their life than petitioner. In addition, literature (Guldner) demonstrates homologous areas between the flu virus for strain B and the antigen recognized in MCTD and, thus, the vaccine probably triggered the MCTD. This is the basis for his theory of molecular mimicry in this case. Id. Dr. Ahmed said that before her September 20, 2012 flu vaccination, petitioner did not have an elevated ESR or CRP. Id. at 112. A high ESR correlates typically with systemic inflammation. Id. at 113. CRP is a more specific marker of inflammation. After petitioner's vaccination, these values were elevated.[93] Id. Dr. Ahmed stated onset of petitioner's MCTD was one-half to two weeks post-vaccination when she had significant fatigue. Id. at 113-14. She had Raynaud's phenomenon 18 months after vaccination. Id. at 114. Dr. Ahmed's opinion is that onset less than six months after vaccination is more likely to be linked to the vaccine. Id. at 114-15. Dr. Ahmed said he is quite confident that MCTD is the correct diagnosis for petitioner at this stage of her disease which could evolve with time. Id. at 115.

Dr. Ahmed said one of the serologic criteria for diagnosing MCTD is anti-RNP antibody. Id. at 130. Petitioner's ANA was positive and continued positive when repeated, telling us that autoimmunity is going on. Id. at 131. He agrees with Dr. Matloubian that petitioner's positive ANA in a homogeneous pattern in 2008 was not caused by the vaccination in 2012. Id. Dr. Ahmed thinks that petitioner did have evidence of autoimmunity in 2008 but had nothing else happening. He said having autoimmunity is not the same as having autoimmune disease. Id. at 132. Dr. Ahmed said he does not know if petitioner's 2008 ANA is the ANA seen in 10 to 20 percent of the normal population and in a homogeneous pattern. Then a subsequent vaccination tipped her over toward autoimmune disease. Id.

Dr. Ahmed agrees that most MCTD patients have a high-titer ANA with a speckled pattern. Id. at 133. He states that petitioner not having autoantibodies other than ANA and anti-RNP antibody does not exclude the diagnosis of MCTD. Id. at 155. If Dr. Ahmed were to

[93] Dr. Ahmed is in error. Petitioner's ESR and CRP were never elevated except for one CRP done on May 14, 2013, which was almost eight months after petitioner's September 20, 2012 flu vaccination. Med. recs. Ex. 3, at 87. On that date, her C3 and C4 complement levels were also high for the first and only time. Id. at 88, 89.

believe that petitioner's MCTD began before her September 20, 2012 flu vaccination, he would say the vaccination significantly aggravated it because she did not have a specific antibody for MCTD before the vaccination and she developed clinical symptoms very shortly after the vaccination. Id. at 161. There is however no medical literature supporting a vaccine significantly aggravating MCTD. Id. at 161-62. There are no reports in the literature of influenza causing MCTD. Id. at 162.

On cross-examination, Dr. Ahmed admitted he is not currently board certified in rheumatology or internal medicine by the American Board of Internal Medicine. Id. at 165. Half of his career (since 2006) has been in research and development for the pharmaceutical companies Novartis, GlaxoSmithKline, and La Roche. Id. at 166. He does not currently maintain a clinical practice where he examines, diagnoses, follows, and treats patients. Id. Dr. Ahmed received an MBA so that he could learn how to run a company. Id. at 170. Dr. Ahmed agreed that Dr. Lin diagnosed petitioner with MCTD based on the positive RNP antibodies and muscle weakness. Id. at 192, 194.

Respondent's counsel asked Dr. Ahmed if he had a patient like petitioner who presented to him on October 31, 2012 with low-titer anti-RNP antibodies, an ANA with a homogeneous pattern, a negative Smith, normal inflammatory markers, no joint swelling, no Raynaud's phenomenon, and no lung involvement, would Dr. Ahmed diagnose her at that point with MCTD based only on the low-titer anti-RNP antibodies. Id. at 197-98. Dr. Ahmed replied, "At that time, I would be suspicious for a mixed connective tissue disease, so I would probably at that time write early – undifferentiated connective tissue disease, if not early overlap syndrome."[94]

[94] Undifferentiated connective tissue disease ("UCTD") "is used to describe a condition in people who have symptoms and lab test results that indicate a systemic autoimmune disorder or connective tissue disease, but which do not meet enough such characteristics to indicate a diagnosis for a well-defined connective tissue disease such as" RA, SLE, or scleroderma. Jessica R. Berman, MD, Undifferentiated Connective Tissue Disease --- In-Depth Overview, HOSPITAL FOR SPECIAL SURGERY, https://www.hss.edu/conditions_undifferentiated-connective-tissue-disease-overview.asp (last visited November 5, 2018). UCTD is "distinctly separate from another group of vague-sounding disorders called overlap syndromes. People with overlap syndromes have the clear features of at least two or more CTDs, and thus may meet the diagnoses for several at the same time. In contrast, patients with UCTD do not have enough of the features of a definite CTD … to be firmly classified with such a diagnosis. However, because they may have a few features from several known diseases, they are said to be 'undifferentiated.'" Id. As many as a quarter of all patients seen by rheumatologists have UCTD. "It is currently believed that less than 20% of patients with UCTD go on to develop a definite connective tissue disease. As many as one in three will experience a remission of their symptoms. The rest continue with generally mild disease in the undifferentiated form." Id. "The hallmark of UCTD is its mild course and low likelihood of progression to a more serious state." Id. Besides a positive ANA, persons with UCTD may have other immunologic abnormalities such as elevated ESR, antiphospholipid antibodies, hypergammaglobulinemia, hypocomplementemia (decreased level of complement, i.e., C3 and C4), anti-dsDNA antibodies, anti-Ro/SSA, anti-SM, anti-RNP antibodies, RF, and anti-Ku antibodies. Id. Petitioner did not have an elevated EST, antiphospholipid antibodies, hypergammaglobulinemia, hypcomplementemia, anti-dsDNA antibodies, anti-Ro/SSA, anti-SM, or RF. She did have anti-RNP antibodies. In one study of persons with abnormalities in the capillaries, 23% progressed to definite scleroderma. "Thyroid disease, especially hypothyroidism (an underactive thyroid gland), is a common autoimmune condition which can be seen more frequently in patients with other autoimmune diseases, such as lupus and rheumatoid arthritis." Id. "Undifferentiated connective tissue disease is most likely to occur in Caucasian women in their 40s-60s." Undifferentiated connective tissue disease, GENETIC AND RARE DISEASES INFORMATION CENTER, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF

Id. at 198.

Respondent's counsel asked Dr. Ahmed if he would have petitioner undergo another test for anti-RNP antibody before beginning treatment with high-dose steroids or Methotrexate if he had seen her on October 31, 2012. Id. Dr. Ahmed responded that if petitioner presented to him with nothing wrong except for the positive anti-RNP antibodies, he would not start any treatment. Id. at 199.

Dr. Ahmed agreed that Enbrel (the transcript spells this as "Embryl"), which petitioner was taking as an immunosuppressant, can cause autoimmune symptoms. Id. Enbrel is a TNF inhibitor. Its generic name is etanercept. Id. He said that no one knows for sure if anti-RNP antibodies are pathogenic or not, but they are associated with rheumatic disease. Id. at 215. U1-RNP is a sine qua non for MCTD, but it is specific not only to MCTD but also seen in other diseases. Id. The five criteria for MCTD in the medical literature specify high-titer anti-RNP antibodies for a diagnosis of MCTD. Id. The authors who coined MCTD do not know how to interpret high-titer anti-RNP antibodies for clinical purposes, but later medical information talks potentially about high-titer anti-RNP antibodies correlating with earlier Raynaud's phenomenon. Id.

Dr. Ahmed said that inactivated vaccines have been killed. Id. at 217. Inactivated flu virus vaccines, such as the ones that petitioner received, are not contraindicated for persons with rheumatic disease. Id. Dr. Ahmed said that the vaccine contained virus that was ruptured and detergent-isolated, and the entire inactivated proteins were administered intramuscularly. Id. at 218. Dr. Ahmed said since petitioner was exposed to all the flu antigens in the split vaccine of Sanofi's Fluzone, and she was susceptible to developing MCTD, the flu vaccination was the environmental factor triggering her MCTD. Id. at 218.

Dr. Ahmed said the major antigen identified with MCTD is either the 68 or 70 kilodalton[95] protein which is called U1-RNP. Id. at 222. There are other fragments of other small RNP and other antigens linked with autoimmune disease. The U1-RNP is seen not only in MCTD, but also in lupus and other autoimmune diseases. Other autoantibodies from other diseases can also cause MCTD. Id. These other autoantibodies could generate some type of ANA positivity. Id.

In answer to the question whether the strain of flu B type vaccine that petitioner received is the same type of the flu B strain virus that Guldner discussed in his article (Ex. 79), Dr. Ahmed answered the strain may not be exactly the same, but a majority of flu sequences are conserved and only a minority of them change annually. Id. at 223. The reason vaccine manufacturers make different flu vaccines annually is that the target responsible for letting flu virus enter is a hemagglutinin ("H") or neuraminidase ("N"). Besides those two proteins, there is a matrix or nuclear flu protein. Id. The proteins that change the most are on the outer surface,

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HEALTH & HUMAN SERVICES, https://rarediseases.info.nih.gov/diseases/12342/undiffferentiated-connective-tissue-disease (last visited November 5, 2018).

[95] Supra n.78.

but the majority of flu virus protein is a conserved sequence. Id. at 224. Dr. Ahmed concludes there would be a high probability that a majority of the flu strain of the flu B strain virus in the Guldner article would also be in the strains of flu viruses used in subsequent vaccines. Id.

The undersigned dispensed with redirect of Dr. Ahmed because of time constraints to allow Dr. Matloubian to testify on direct and cross-examination.

Dr. Matloubian testified for respondent. Id. at 229. Not only is he a rheumatologist, he also has a doctorate in virology. Id. at 230. He spent four years in a laboratory studying immune responses in mice to acute and chronic viral infections. Id. Since 2004, he has been at UCSF and is currently an associate professor there. Id. at 31. At UCSF, he sees rheumatology patients from all over the world. UCSF is a tertiary referral center. Dr. Matloubian has his own rheumatology practice as well. Id. He evaluates patients and is responsible for their diagnosis and treatment. Id. at 232. He has been doing this for about 16 years, since 2001. His areas of expertise are rheumatology and immunology. Id. For the past 16 years, he has attended inpatient consult service for rheumatology at UCSF to work up patients with a fellow and arrive at a diagnosis and treatment. Id. at 238-39.

On a daily basis, Dr. Matloubian devotes 40 percent of his time to clinical activity, 50 percent to research, and 10 percent to administration. Id. at 233. Every week, Dr. Matloubian sees four new patients along with follow-up patients. The new patients are referred from general medicine clinics or outside physicians or another rheumatologist for a second or even a third opinion. Id. Among those rheumatology patients are those with MCTD. Id. at 234-35. Dr. Matloubian said that rheumatology is a group effort. Id. at 236. As is apparent from petitioner's medical records, different rheumatologists see the same person on different days and have different diagnoses. Objective clinical findings are not as objective as desired. Id. A medical director at a pharmaceutical company does not see patients on a daily basis and follow them longitudinally. Id. Dr. Matloubian has written peer-reviewed articles on immunology and lectured in immunology. Id. at 237. Immunomodulating agents can cause autoimmunity. Id. at 238. Dr. Matloubian is associate director of the Molecular Medicine Consult Service for patients with multisystem diseases affecting multiple organs. Id. at 239.

Dr. Matloubian's opinion in this case is that flu vaccination on September 20, 2012 did not in any way affect whatever petitioner's current condition is. Id. at 241. He thinks petitioner's hypothyroidism is significant. Id. at 242. In the US, the most common cause of hypothyroidism is autoimmune thyroiditis. This is especially true when someone, as petitioner's mother, has autoimmune thyroiditis or Hashimoto's thyroiditis. Id. People with autoimmune disease are more likely to have another autoimmune disease, such as thyroid disease. Id. at 243. Dr. Matloubian said that petitioner's relevant symptoms prevaccination were musculoskeletal. She had injury-related back pain in 2000 which Dr. Saal treated from 2001 to 2008. Id. She had shoulder pain and tendinitis, plus an MRI of her bilateral ankles which showed evidence of adhesions causing her pain. Id. at 143-44.

On March 7, 2011, petitioner had right foot pain and bilateral shoulder pain. Id. at 244.

In 2006, a doctor noted petitioner had numbness in her right fingers and was tight everywhere with frequent right arm pain. In a patient health questionnaire in 2007, petitioner wrote she had pain in both hands and her neck. Two months later, she noted she had shoulder pain as well. In March 2008, her PCP noted petitioner was complaining of one month of aching fingers bilaterally and the doctor did blood tests to rule out autoimmune disease. Id. Dr. Matloubian said in his practice at UCSF, the doctors make a decision whether or not a patient in pain has an autoimmune disease and do blood tests. Id. at 244-45. Petitioner did not file any records from the rheumatologist she saw in 2008. Id. at 245. Dr. Matloubian asked on what basis did that rheumatologist in 2008 diagnose petitioner with osteoarthritis as opposed to an autoimmune disease or inflammatory arthritis. We do not know what blood tests the rheumatologist ordered.

Dr. Matloubian also noted that petitioner had pre-vaccination complaints of fatigue. Id. Summing up, he said petitioner had fatigue, musculoskeletal pain in many joints, including her hands, and tightness and numbness in her hands, predating by many years her 2012 vaccination. Id. at 245-46.

Regarding myalgias vs. myositis, Dr. Matloubian said that myalgia is muscle pain without muscle inflammation. Id. at 246. Myositis is muscle inflammation sometimes seen in MCTD. In order to diagnose myositis, one needs laboratory evidence of inflammation, which would be elevated creatine kinase ("CK") and elevated aldolase, both of which are muscle enzymes, and elevated liver enzymes. Id. Another way to diagnose myositis is to do an MRI or an EMG/nerve conduction study. Id. at 247.

Dr. Matloubian said petitioner had flu vaccine in 1999, 2009, and 2012. Id. As Dr. Ahmed said, the sine qua non of having MCTD is high-titer anti-RNP antibodies. Id. at 251. High titer means 1281 or 1280 or higher. Without high-titer anti-RNP antibodies, someone cannot diagnose MCTD. Dr. Matloubian and his colleagues at UCSF require two things to diagnose MCTD: anti-RNP positivity and Raynaud's phenomenon. Id. When making an accurate diagnosis, he is a splitter, not a lumper. Id. at 252. It is important to make an accurate diagnosis because the patient wants to know his or her prognosis. When it comes to treatment, he is a bit of a lumper, as is everybody else, because the toolbox for treating people with multiple diseases is limited. Id.

Dr. Matloubian said that doctors really do not understand what causes MCTD, lupus, or RA. Id. at 253. If someone is a smoker, her risk of RA increases by 60 fold.[96] Id. at 254. He said that is significant. Id. He does not think MCTD is multiple different autoimmune diseases. Id. at 255. MCTD has different genetic risk factors than the genetic signatures for lupus, scleroderma, dermatomyositis, and polymyositis. Id.

Dr. Matloubian said the reason the pattern of ANA is important is that the pattern correlates with specific antigens the lab is testing. Id. at 256. The ANA in Hashimoto's thyroiditis has a homogeneous pattern, not a speckled pattern. Id. at 257. Petitioner had a homogeneous pattern on the two different occasions, four years apart (2008 and 2012), and her

[96] Petitioner was a smoker. Med. recs. Ex. 3, at 109.

ANA was tested by two different laboratories with two different lab personnel interpreting the test results. Id. Regarding Dr. Ahmed's view that a homogeneous result can mask a speckled result, Dr. Matloubian said that would have to be a low-titer speckle. Id. Dr. Matloubian also said that the ANA titer of 1:320 measured in 2012 vs. the ANA titer of 1:160 measured in 2008 is only one dilution difference, which is not clinically significant. Id. at 258.

Dr. Matloubian explained that a lab technician is obligated to continue diluting the ANA until he or she does not see fluorescence any more. Id. at 257-58. When petitioner's ANA titer was tested in 2012 as 1:320, it means it lost fluorescence somewhere between 320 and 640. Id. at 258. That means if there were a speckled pattern that the homogeneous pattern was masking, the speckled pattern was either 320 or less, because if it were more than 320, as the lab technician diluted the homogeneous antibody away, he or she should have been able to see the speckled pattern. Id. Dr. Matloubian said that if the speckled pattern had been present, it would be important because a diagnosis of MCTD requires high-titer anti-RNP antibodies. Id. at 259. That high titer has to be speckled. The reason it has to be speckled is it corresponds to anti-RNP antibodies. The target antigen, i.e., RNP, is a protein and RNA complexes in the nucleus are involved in processing RNA made from DNA. They are in small locations processing genes, which is why the pattern appears speckled. The homogeneous pattern is against the DNA or the chromatin, which is everywhere, and that is why the pattern is homogeneous in the nucleus. Id.

Dr. Matloubian said that a positive ANA in the absence of other autoantibodies is insufficient to diagnose rheumatic disease. Id. In order to have a diagnosis of rheumatic disease with a positive ANA, someone needs a positive subserology. Id. at 259-60. For example, in SLE, someone will have either anti-double-stranded DNA or anti-Smith or Smith-plus-RNP. Id. at 260. In Sjögren's, someone will have SSA, SSP antibodies that are positive. In MCTD, someone will have anti-RNP antibodies but not Smith. In scleroderma, someone will have other positive antibodies. Id. However, Dr. Matloubian said someone can have positive ANA and anti-RNP antibodies without having clinical symptoms. People can have multiple antibodies for years without having symptoms. Therefore, a doctor has to interpret the results of antibody testing in the right clinical setting. Id.

Dr. Matloubian said if someone came to him without inflammation on physical examination, and had normal laboratory values on testing but a positive ANA and positive anti-double-stranded DNA or positive anti-Smith plus RNP, he would examine the person very carefully. Id. He would check the patient's urinalysis, and all organ system that the disease could affect for objective data. Id. If the data were negative, he would reassure the patient that at that point in time, the patient did not have an autoimmune disease. Id. at 260-61. But he also would tell the patient that, at some point in the patient's life, the patient may develop autoimmune disease. Id. at 261. It could take 20 years to develop autoimmune disease. There is no data that just because the patient has autoantibodies, the patient is more prone to getting an autoimmune disease because of environmental exposure. Dr. Matloubian said that was very speculative. Id.

Dr. Matloubian's opinion is that petitioner's positive anti-RNP antibody titer in 2012 was

a false positive. Id. When the lab technician does the multiplex bead assay, there is not only an RNP bead, but also there is one bead called Smith plus RNP. Id. at 262. The Smith antigen is a totally different antigen than the RNP antigen. If someone were positive for anti-RNP antibodies, the bead for anti-Smith plus RNP should also be positive. In petitioner's case, her anti-Smith plus RNP was negative, which means a lower probability of her having an autoimmune disease. Moreover, the anti-RNP antibodies did not have a speckled pattern. Id. But that is in addition to the contradiction of the anti-Smith plus RNP being negative yet the anti-RNP antibodies being positive. Id. Either the anti-RNP antibodies are a false positive or an extremely low titer. Id. at 262-63.

Dr. Matloubian said if he had seen petitioner at his clinic, he would have tested the antibody again. Id. at 263. Kaiser (petitioner's HMO) only does the bead assay, as do Quest and Lab Corp and others. But in Dr. Matloubian's laboratory at UCSF, and in ARUP labs, to which Dr. Ahmed referred, they do an ELISA assay which is more sensitive and more specific for detecting anti-RNP antibodies. That is important because it gives him the correct information to tell the patient whether or not she has MCTD. Id. The highest range for anti-RNP antibodies is eight. Patients Dr. Matloubian has seen with MCTD have had anti-RNP antibodies higher than eight. Id. Medical literature shows patients with MCTD with serology tested by bead assay who had an ANA done with results of eight plus antibodies. Id. at 264.

Petitioner's second rheumatologist, Dr. Lau, said twice in his report RNP-positive but no titer. Id. at 265. Dr. Lau also notes RNP-Smith ENA negative. He thought the results could represent possible overlap syndrome, even MCTD, as her RNP was positive though no titer. Id. Petitioner's third rheumatologist, Dr. Patel commented he did not have petitioner's medical records. Id. at 266. Dr. Matloubian commented that Dr. Lin did not note during an examination of petitioner that she had sclerodactyly or synovitis. Id. at 267-68. One week later, Dr. Lau examined petitioner and noted she had synovitis but not sclerodactyly. Id. at 268. Dr. Matloubian admitted there is a lot of subjectivity among rheumatologists. He said in diagnosing, rheumatologists need to rely more on objective modalities. Id.

Petitioner never had an elevated inflammatory marker even when she was in between treatments except for one time she had a C-reactive protein of 0.7 when the cutoff is 0.5. Id. at 269. She never had an elevated sedimentation rate. Dr. Matloubian had an MCTD patient the prior week and her C-reactive protein was 74. She obviously had inflammatory disease. Id. Another sign that Dr. Matloubian seeks as objective proof of inflammation is anemia of chronic disease. People with autoimmune rheumatic diseases have low-grade anemia. Petitioner's hematocrit was about 43, 44, which is very good for someone with presumed autoimmune disease. Another objective marker of inflammation is platelet elevation, i.e., platelets go up when someone has systemic inflammation. He sees that all the time in his rheumatoid arthritis patients especially at the time of diagnosis. But, petitioner never had elevated platelets. Id. Petitioner had documented synovitis only once which Dr. Lin noted. Id. at 269-70. Otherwise, all the medical records state is how petitioner said she was feeling. Id. at 270.

The one time petitioner had an elevated C-reactive protein, Dr. Matloubian said petitioner

could have had an infection and her C-reactive protein was slightly elevated as an acute phase reactant. She could have had sinusitis, a urinary tract infection, or a cold, and that could have elevated the C-reactive protein a little bit. Id. When petitioner first presented in October 2012, her lab results were absolutely normal, yet that is when Dr. Lin diagnosed her with MCTD. Id. Petitioner had multiple CK level tests and they were always normal. Id. at 272. Her liver function tests were always normal. She never had myositis (inflammation of muscles). Myalgia (muscle pain) is nonspecific. Myositis is very specific. Id. As part of that muscle inflammation, a patient releases muscle enzymes, CKs, which can be detected in blood tests. Id. at 272-73. Petitioner had two tests for two different muscle enzymes, CK and aldolase, when she saw Dr. Lin the first time. Id. at 273. Both her CK and aldolase levels were normal. Her liver enzymes were normal, too. Petitioner had three independent measures of muscle inflammation and they were all negative when Dr. Lin saw her on October 31, 2012. What was key to Dr. Matloubian is that petitioner did not have weakness on physical exam. Id. at 274. If she had had myositis, she would have been weak. Id.

Dr. Matloubian said he does not know what petitioner has. He has not seen clear evidence that she had autoimmune disease when she first saw Dr. Lin on October 31, 2012. When she saw Dr. Lin, her laboratory values were fine. Dr. Matloubian said he does not know why petitioner got better. Thirty percent of patients in clinical trials for rheumatoid arthritis have a placebo effect. Id. That is a nonobjective measure. Id. at 275. When someone gets an IV infusion, there is some placebo effect. The target of Actemra is interleukin-6 ("IL-6") and the driver of elevated C-reactive protein is high IL-6 levels. But petitioner did not have high C-reactive protein levels and only once, in May 2013, did she have a slight elevation. Therefore, Dr. Matloubian does not understand why petitioner would respond to anti-IL-6 medication, i.e., Actemra, when IL-6 elevates C-reactive protein and she had normal C-reactive protein. Id.

The undersigned asked Dr. Matloubian what he meant when he said he does not know what petitioner had since in his reports, he said she has chronic pain syndrome, osteoarthritis, and autoimmune thyroid disease. Id. Dr. Matloubian said her rheumatologists think there is something different about her fingers, one saying sclerodactyly and another saying puffy synovitis. Id. at 276. If she had sclerodactyly, that would be due to deposition of collagen, causing the skin to get tighter. That does not go away with any therapy. Id. If there were changes in petitioner's skin, an MRI or ultrasound would really help figure out if she has actual inflammation or some other process. Id. at 277. Dr. Patel wondered if petitioner had seronegative rheumatoid arthritis and suggested petitioner stop taking Actemra and see what happens. Id.

Petitioner's pre-vaccination records do not document a hand examination showing sclerodactyly. Id. at 278. On October 31, 2012, Dr. Lin documented some painful joints but no joint inflammation. Id. at 278-79. Dr. Lin noted no swollen joints, no synovitis, no tenosynovitis, and no muscle weakness or tenderness. Id. at 279. Dr. Matloubian said he would not have diagnosed petitioner with MCTD, unlike Dr. Lin, based on the serology and physical examination of petitioner on October 31, 2012. Id. at 280. He would have repeated her autoantibody tests. He would have repeated the RNP test with a different assay, sending the test

to ARUP labs which does it by ELISA. It does not mean petitioner would not have developed an autoimmune disease several years later, based on the Arbuckle paper that Dr. Ahmed discussed. Someone can be ANA positive and 10 or 20 years later develop an autoimmune disease. Id.

Dr. Matloubian said he would not have prescribed Prednisone (a steroid) for petitioner as Dr. Lin did on October 31, 2012 because it has a lot of side effects and people always feel better on it. Id. at 281. Feeling better does not mean the patient has autoimmune disease. Referring back to the two different titer measurements in 2008 and 2012 for ANA, Dr. Matloubian said these tests were done at two different laboratories and, as Dr. Ahmed said, the results depend on the lab technician. One person can call the titer 1:160 and another person can call it 1:320. It is not a significant change. Id. Several exhibits filed in this case state there is no correlation between ANA value and disease activity. Id. at 282. Autoantibodies are not pathogenic or disease-causing, except for anti-double stranded DNA in lupus. Id. at 284. Johns Hopkins, who are experts in anti-U1-RNP, state that anti-RNP levels have nothing to do with disease activity, which means they are not pathogenic. Id. at 286. ANA and RNP are used for diagnostic purposes in the right clinical setting. Id. at 287. When petitioner saw Dr. Lin on October 31, 2012, petitioner had no objective clinical finding of an autoimmune disease. She did not have Raynaud's phenomenon. She did not have anything else that would point to MCTD or inflammatory arthritis. Id.

ANA and RNP are markers of disease. Id. at 288. Dr. Matloubian disagrees with Dr. Ahmed when he said that the prime boost with ANA brought it to 1:160 and the flu vaccine in 2012 boosted it to 1:320. But that is of no clinical significance. The ANA and RNP are not what is causing disease. They are markers of disease. Id. Even if there were molecular mimicry between flu B virus and RNP, making antibody to RNP is irrelevant because anti-RNP antibodies do not cause disease. Id. In contrast, group B strep antibodies cross-react to some heart muscle protein, causing damage, which shows molecular mimicry. Id. at 289. Mothers who have anti-SSA antibodies can cause heart disease in the fetus by crossing the placenta, showing those antibodies are pathogenic. Id. Someone with Graves disease, which is antibody-mediated, can have antibodies crossing the placenta to the fetus and cause neonatal thyroiditis. Id. at 289-90. Those antibodies are clearly pathogenic. Id. at 290. Similarly, someone with anti-double-stranded DNA could have kidney damage because the antibody is pathogenic to the kidneys. Id.

Dr. Matloubian said that in order for Dr. Ahmed to use the theory of molecular mimicry here, Dr. Ahmed would have to show it produces the outcome and that the outcome causes the disease. Id. Dr. Matloubian could not find any medical literature associating influenza infection and MCTD. Id. at 293. He said since there is no association between the natural flu infection and MCTD, one cannot extrapolate that a vaccine drawn from flu virus can cause true molecular mimicry where the original infection cannot. Id. The American College of Rheumatology does not advise against vaccinating people who have lupus, rheumatoid arthritis, dermatomyositis, or MCTD with inactivated flu vaccine. Id. at 296.

Referring to Dr. Ahmed's article (Ex. 57) on whether there is a relationship between

adjuvanted vaccines and autoimmune disease, Dr. Matloubian said the key to fear of vaccination is that it is based on speculation. Id. at 298. He said there is no preponderant evidence proving that flu vaccine caused petitioner's condition. Id. at 299. Dr. Matloubian pointed to page 2 of Dr. Ahmed's article on adjuvanted vaccines and autoimmune disease in which the authors say that infection, but not vaccination, can exacerbate preexisting autoimmune disease. Dr. Matloubian stated that in spite of Dr. Ahmed's testimony speculating that when people who are genetically predisposed develop autoimmune disease when they get an infection or receive a vaccination, preponderant evidence shows that people already with autoimmune disease do not have a worsening of their symptoms after vaccination. Id. at 299-300.

Dr. Matloubian said part of the reason people connect vaccination to worsened autoimmune symptoms is that we do not really understand immunology. Id. at 300. Dr. Ahmed continues in his article that there is the risk of coincidental association of a naturally-occurring autoimmune disease and vaccination. Id. Dr. Matloubian said that the bottom line is that someone who is autoantibody positive may develop autoimmune disease at any time. Id. at 300-01. If the person receive a vaccination, the vaccination could be coincidental to the onset of the person's autoimmune disease. Id. at 301. There is really no way of positing causation either in a rheumatologic practice or in a clinical trial of a drug. Id.

Dr. Matloubian said the probability that autoimmune disease may begin months or years before clinical diagnosis poses logistical challenges. Id. at 302. How do we know petitioner was not progressing toward clinical symptoms just at the time she received flu vaccinated in 2012? Id. Dr. Matloubian said that petitioner did not have Raynaud's phenomenon until two years after she received flu vaccine and therefore it is purely coincidental rather than causal. Id. at 302-03. Dr. Matloubian emphasized that Dr. Ahmed's medical article (Ex. 57) was peer-reviewed and published. Id. at 303.

Dr. Matloubian noted that none of petitioner's treating doctors stated that flu vaccine caused her condition. Id. at 304. Petitioner wrote a letter to Dr. Tsai (Ex. 10, at 1) asking him to state flu vaccine caused her MCTD. Dr. Tsai was very diligent. He did a literature search and documented what literature he read. Based on his review of the medical literature, Dr. Tsai concluded that no publication showed flu vaccine causes MCTD. Id.

Dr. Matloubian summed up his opinion that it is unclear if petitioner had MCTD because when she saw Dr. Lin on October 31, 2012 within weeks of flu vaccination, petitioner did not have inflammatory arthritis, Raynaud's phenomenon, joint swelling, or laboratory abnormalities of a systemic inflammatory disease. Id. at 311. Petitioner never had lung involvement. Id. Dr. Matloubian said more likely than not, petitioner did not have MCTD, especially since the hallmark of MCTD is having high-titer anti-RNP antibodies. Id. at 312.

As for petitioner's recent nailfold capillary testing. Dr. Matloubian went to an expert, Dr. Bowen, who is director of the UCSF scleroderma center. Id. at 313. Before joining UCSF, Dr. Bowen was at Johns Hopkins. He sees only scleroderma patients. Id. Dr. Bowen is very diligent and used a pocket magnifying glass with a light to look at petitioner's nailfold

capillarscopy. Id. at 313-14. Dr. Matloubian told Dr. Bowen the context that this concerned a 60-year-old woman diagnosed with MCTD who had an ANA of 1:320 and an anti-RNP antibody titer of 1.2 by multiplex assay but negative for all other serologies. Id. at 314. Dr. Bowen looked at petitioner's nailfold capillarscopy and said he could not tell anything because it was out of focus. He could not tell where he was in the nailbed capillaries. Dr. Matloubian said if you looked at the normal photos in multiple exhibits, you would not know what you were looking at. You start from the bottom and see these nice capillary loops going up. In these photos, you are not sure where you are looking. It is not from the same direction. The photos are out of focus and there seem to be a lot of blotches. Dr. Bowen said that he did not think much of petitioner's nailfold capillaroscopy. Id. Dr. Matloubian added Dr. Bowen is an expert in the area. Id. You just cannot diagnose from pictures alone. Id. at 315. You need experience. Id.

Dr. Matloubian then said that Dr. Bowen said something that surprised Dr. Matloubian. Id. He said that you have to be careful the person has not had a manicure for two weeks or so before doing this nailfold capillaroscopy. Dr. Matloubian found a paper in which the author says to be very careful because if a patient had a manicure or was a nail-biter or played guitar, he or she was having nail trauma all the time and can appear to have nailfold capillary changes. Thus context is very important. Id. Dr. Matloubian said that from the very beginning of the case, he pushed for petitioner's sake that she go to either Stanford and mention the doctor's name or go to UCSF and see Dr. Bowen because these people are much better at this than anybody else that Dr. Matloubian knows. Id. at 315-16.

Dr. Matloubian doubts that petitioner has Raynaud's phenomenon because the records do not record distinct color changes in her fingers. Id. at 316. Dr. Ahmed during his testimony did an earlier demonstration but of arteries in the wrist. Id. Dr. Matloubian said that the arteries in the wrist are not involved in Raynaud's; the digital arteries are involved in Raynaud's. Id. Petitioner described tingling and numbness in her fingers, but not color changes. Id. at 317. Dr. Xu diagnosed petitioner with neuropathy. Id. Raynaud's affects the digital arteries in the fingers and the toes. Id. at 318. Dr. Matloubian mentioned that when Dr. Ahmed wrote in his first expert report that Raynaud's caused numbness at the bottom of the feet, Dr. Matloubian was very shocked because the numbness affects the digital arteries. Id. In photos of petitioner's fingers, there is no sharp demarcation of coloration. Id. at 319. There is some shadowing, but that may be due to how the photograph was done. Id.

Dr. Matloubian repeated that anti-RNP antibodies are not pathogenic, meaning they do not cause MCTD or any other disease. Id. at 320. He does not agree that there is molecular mimicry between the genetic components of flu virus infection or vaccine and MCTD. Id. at 320-21. When a person receives a vaccination, you can boost the response with another vaccination because the primary response forms a memory. Id. at 321. The hallmark of a memory response is antigen specificity and rapidity. Id. at 322. The point is true for a foreign antigen but not for a self-antigen or molecular mimicry. Someone with a chronic infection does not form good immunological memory. The cells primed with initial infection are being primed continuously. To form good memory, you need to have the antigen to what caused the initial

priming to go away. Id. If you continually stimulate with that antigen, you do not form good memory. Id. at 322-23. When people talk about breaking tolerance through molecular mimicry with a priming immunization, then the B cell or T cell that is seeing the vaccine component is going to see self-antigens and never become a good memory. Id. at 323. Dr. Matloubian does not see how prime/boost works in that situation. If, as Dr. Ahmed said, the 2012 vaccine was a boost, then that should have recalled a memory response and petitioner should have had symptoms or disease within two days, not two weeks. The fact that it took her two weeks for symptoms does not fit in with memory or booster response. Id. Dr. Matloubian does not think there is any evidence supporting a causal relationship between flu vaccine and petitioner's alleged MCTD. Id. He also does not think there is support for petitioner's allegation that her September 2012 vaccination significantly aggravated her underlying autoimmune disease that was asymptomatic until October 2012. Id.

Dr. Matloubian observed that Dr. Lin recorded petitioner's hand pain began in August 2012. Id. at 326. Dr. Lin documented that what she considered might be inflammatory hand pain with prolonged morning stiffness started in August 2012. Id. Dr. Matloubian noted the symptoms seemed the same pre- and post-vaccination to Dr. Lin. Id. at 326-27. Dr. Lin corrected her October 31, 2012 medical record regarding the onset of petitioner's symptoms two and one-half years after October 31, 2012. Id. at 328.

On cross-examination, Dr. Matloubian said the most common type of hypothyroidism in women in the United States is autoimmune thyroiditis or Hashimoto's thyroiditis. Id. at 335. The only other causes of hypothyroidism are radiation and medications for people with Graves' disease or hyperthyroidism. They get medications that can make them hypothyroid. Id. Dr. Matloubian disagreed that the vast majority of patients who have autoimmune thyroiditis have a speckled ANA pattern. It is a homogeneous pattern. Id. High-titer anti-RNP antibodies are part of the diagnosis for MCTD. Id. at 336. In the absence of clinical signs and symptoms of inflammation, Dr. Matloubian said he "would be very, very hesitant to interpret a borderline RNP antibody test, especially when the RNP-plus Smith is negative as being positive and [an] indicator of mixed connective tissue disease without any evidence of that disease at the time of diagnosis." Id.

Dr. Matloubian said that titers of anti-RNP antibodies can fluctuate without having any relationship with disease activity. Id. at 337. But, at the time of diagnosis, based on all the criteria for diagnosing MCTD, the anti-RNP antibodies must be high titer. He noted that petitioner quit smoking[97] in April 2013. Id. Dr. Matloubian agreed that MCTD has signs and symptoms that may develop over months and years. Id. at 338. Dr. Matloubian said there is something like urban legends called chart lore. Id. at 350. It is also called diagnostic momentum. This is when someone makes a diagnosis and it gets carried through the medical charts to each of the subsequent physicians who see it. In his practice, Dr. Matloubian needs to analyze all the data that are given to him in their context. Id. Then he sees discrepancies in the physical examinations among petitioner's three rheumatologists and wonders whom to believe.

[97] On March 11, 2010, petitioner told her PCP she was ready to stop smoking. Med. recs. Ex. 14, at 29. On May 30, 2013, petitioner told Dr. Tsai that she had quit smoking one month earlier, i.e., April 2013. Med. recs. Ex. 3, at 109.

Id. at 350-51. Should he believe Dr. Lin's physical exam, or Dr. Lau's one week later, or Dr. Patel's? Id. at 351. One doctor sees sclerodactyly; the other does not see it. One sees synovitis; the other does not see it a week before. Dr. Matloubian said these discrepancies put him in a hole to make a diagnosis and assessment based on what the records document, which is not an easy job. Id. There is no internal consistency in these records. Id.

Dr. Lin used terms to describe the photos of petitioner's capillaroscopy: dilated capillary loops, tortuous loops, vascular congestion, slow blood flow, RBC aggregation. Id. at 352. Dr. Matloubian said these are not the usual terms doctors use to describe a capillaroscopy. Id. Dr. Matloubian really doubts that Dr. Lin has a lot of experience doing capillaroscopy because this was 2017 and Dr. Lin diagnosed petitioner in 2012. Id. at 352-53. At any time during this interval, Dr. Lin could have taken out the ophthalmoscope as Dr. Ahmed said and visualized petitioner's nail beds, i.e., done a nailfold capillaroscopy. Id. at 353. But she did not do it. Id. Petitioner said in her affidavit that Dr. Ahmed suggested Dr. Lin do a nailfold capillaroscopy. Dr. Matloubian had suggested in his expert report that petitioner should have it done. Id. (At this point, Dr. Matloubian left the hearing room to catch a plane.)

Petitioner's husband testified next for petitioner. Id. at 355. He described petitioner's reaction to her flu vaccination in 1999 as immediate and as a frozen shoulder. Id. at 356. She had extreme shoulder pain and the symptoms lasted close to a year. Id. He said the main symptom was migraine headaches that offensive odors triggered. Id. at 356-57. Petitioner had another flu vaccination in 2009 and did not have an adverse reaction to it. Id. at 357.

Petitioner received flu vaccine on September 20, 2012 and, about one and one-half weeks later, she complained of severe pain in her knees, extreme fatigue, and joint stiffness in her hands. Id. Petitioner's husband said petitioner was working a day shift. Id. Before the vaccination, she had been in pretty good health. Id. at 358. She had a back injury in 2000 and she returned to work in 2006. Id. After September 20, 2012, when petitioner's husband came home from work, he would find that his wife got home before him and went to bed until 10:00 or 11:00 p.m. Id. at 359. She complained of extreme fatigue. When she got up for a while, she would go back to bed. Id. Besides sleeping a lot, petitioner told him she had extreme pains in her knees and it was very difficult for her to get around. Id. Petitioner told him she could not get up the steps of the parking garage when she went off her work shift. Id. at 360. She also told him she was having trouble with her hands and could not grip a pen to document her work after her shift. Id. He needed to take up the slack in household chores that petitioner could no longer do, including cooking and yard work. Id.

Petitioner's husband said that steroids gave his wife some improvement. Id. at 362. She did not get a whole lot of relief from the biologics, Enbrel and Orencia. She went on short-term disability. Id. Petitioner complained about tingling and numbness in her extremities which was pronounced in the winter. Id. at 363. She made a trip to Cleveland in January 2013 to care for her mother and had just come in out of the cold when she saw her fingers were whitish purple. Id. at 363-64. She also complained of numbness and tingling in her toes. Id. at 364. The methotrexate caused hair loss and nausea. Plaquenil or hydroxychloroquine required her to

minimize her exposure to sunlight. Id. Actemra is giving petitioner significant relief. Id. at 365.

Petitioner testified next. Id. at 369. She previously was a nurse at the Valley Medical Center. Id. at 370. She was on interventional radiology when she suffered a back injury while catching a patient who was falling off a table, which ended that job and put her on bed rest for five years. Id. at 371. She received flu vaccine in 1999. That night, her upper arm had huge swelling and she could not lift it. Id. She went to the Valley Medical health center which diagnosed her with shoulder impingement. Id. at 371-72. She applied for workers compensation. Id. at 373-74.

Her next flu vaccination was in 2009. Id. at 374. She did not have any adverse reaction to it. Id. "That was wonderful. I breezed right through that one." Id. at 376. She said she was only an occasional smoker. Id. at 378.

In September 2012, she received her next flu vaccination and life was normal for the next week and one-half or so. Id. at 378-79. She noticed she was exhausted and could not keep up with what she had been doing for months before then. Id. at 379. She had trouble holding her pen when she was trying to fill out a chart. She found spiking a bottle or spiking a bag for an IV was hard. Her fingers looked like fat little sausages and hurt. Typing became more and more difficult. When she got home, she would go straight to bed. At times, she did not get out of her nurse's uniform. She had a debilitating weakness. Id. She was sore all over. Id. at 380. She would lie in bed until 10:00 or 11:00 p.m., change into her pajamas, and go back to bed until the next morning. When she would get home from work, her knees hurt so much, she put frozen peas on them to get the swelling down. She would get a bucket of ice water and put her hands in to make them feel better. Sometimes she would use heat by putting warm rice in the microwave and put her hands through the rice. She would sit in the hot tub to feel better. Id.

She made an appointment with Dr. Xu, her personal care physician, and told her what her symptoms were. Id. at 381. She told her the pain was in her hands, wrists, ankles, knees, and everywhere. She complained of acid reflux. She said she was incredibly tired and sore. She told Dr. Xu she could not grip a pen and steering a car and opening doors was hard. Id. Odors would set off her migraines. Id. at 382. Dr. Xu told petitioner she was concerned about rheumatoid arthritis and had her take tests and referred her to a rheumatologist at Kaiser. Id. at 383.

Petitioner saw Dr. Lin and could barely grip the steering wheel when she got to the appointment. Id. She told Dr. Lin about having trouble keeping up with work, not being able to hold a pen and write or do her work activities, about her knees, feet, and ankles hurting, and getting the flu shot and becoming bone tired, i.e., very exhausted. Id. Dr. Lin asked petitioner if anyone in her family had an autoimmune disease. Id. at 384. Petitioner told her she had a family history of Hashimoto's. Both her mother and a couple of sisters have Hashimoto's. Her brother has rosacea. Dr. Lin asked her about the redness on her face and petitioner said she had been told she has rosacea. Then, Dr. Lin examined her hands and asked if she always had thick fingers. Petitioner told her no, and these were like sausages. Dr. Lin was trying to pinch the skin

of each of petitioner's fingers. Id.

As for petitioner's rosacea, she said that she had the rash for a while as a young girl and it never got really bad. Her brother's rash got bad with raised papules, but she never had that. Id. Eventually, a dermatologist diagnosed her with rosacea. Id. at 385. It was not over the nose as the butterfly rash with lupus. She had laser surgery done to reduce the redness. That might have occurred in 2016. Id.

When she first started seeing Dr. Lin, Dr. Lin was concerned about different disease diagnoses every time petitioner went. Dr. Lin would check petitioner's face and fingers. Id. at 386. Dr. Lin was worried petitioner had lupus, Sjögren's, or RA. Dr. Lin told petitioner that as far as she could see, petitioner had little bits of each disease but the lab tests did not necessarily show that. Therefore, Dr. Lin was treating her symptoms, swollen hands, and knees. Dr. Lin told petitioner her lab results were not remarkable, just a little elevated, but Dr. Lin was treating what she saw and found on examination. Id. Dr. Lin was treating petitioner's swollen joints and Dr. Lin said this was a disease that would progress, and sometimes it would be RA and sometimes it would become lupus or something else. Id. at 386-87. Dr. Lin said she did not know, but if she could stop it right then with treatment, it might not progress. Id. at 387. Petitioner said she told Dr. Lin at the first appointment with her that petitioner's fingers had turned white and purple when she was in Ohio in January during a bad storm.[98] Id. She notices that her feet in winter hurt with pins and needles, as if they were burning. Id. at 387-88. The undersigned asked petitioner if she were talking about her feet or her toes. Id. at 388. She replied she meant her toes. Id. She said her feet were always kind of reddish. Id. at 389.

In the beginning of her seeing Dr. Lin, petitioner said she was seeing her almost weekly, coming back with some other drug treatment. Id. at 391. After Mexotrexate, Dr. Lin suggested trying Orencia, but that had minimal results. Id. at 392. Petitioner's neighbor's daughter had juvenile rheumatoid arthritis and was on Enbrel. Petitioner asked Dr. Lin if she could take Enbrel. Dr. Lin said okay. Enbrel seemed to help for a little bit, but then suddenly stopped helping. Dr. Lin suggested an infusion, to which petitioner agreed. Id. That is when petitioner started monthly infusions of Actemra,[99] which she loves. Id. at 393. A week or a few days before her infusion, she starts getting stiff and swollen again, and she looks forward to getting the Actemra infusion. She said that she never applied for workers compensation for her alleged vaccine injury because of her bad experience with workers compensation when she hurt her back. Id. Petitioner retired after her flu vaccination. Id. at 397.

[98] This statement appears erroneous since petitioner did not have cold fingers until she saw her mother in January 2013. Ex. 7, at 3 (petitioner's first affidavit). Petitioner's first appointment with Dr. Lin was October 31, 2012. Starting on August 19, 2013, Dr. Lin began noting that petitioner did not have Raynaud's phenomenon. Med. recs. Ex. 3, at 125. On March 28, 2014, Dr. Lin noted petitioner did not have Raynaud's. Id. at 163. On November 19, 2014, Dr. Lin noted petitioner did not have Raynaud's. Id. at 192. On January 5, 2016, Dr. Lin noted petitioner did not have Raynaud's. Med. recs. Ex. 10, at 1.

[99] Actemra is for adults with moderately to severely active RA who have used one or more disease-modifying antirheumatic drugs (DMARDS), such as methotrexate, which did not provide enough relief. ACTEMRA TOCILIZUMAB, www.actemra.com (last visited Nov. 15, 2018).

Petitioner then explained her request to Kaiser for changes to her medical records. Id. at 399. When she read her medical records, she found a lot of incorrect information there. Id. She said she told Dr. Xu and Dr. Lin that her problem with her hands had just happened within the prior couple of weeks. Id. at 400. She said she told Dr. Lin she had gotten the flu shot and the hand problem had occurred three to four weeks before she saw Dr. Lin. But Dr. Lin's notes said her problem had been going on for a few months. Petitioner hand-delivered a letter to the medical records department to remind Dr. Lin of the onset, but the medical records department would not accept the letter or deliver it to Dr. Lin. Id. The medical records department required petitioner to put the letter in writing to an intermediate person and the person called her, but she did not understand his accent. Id. at 401. She did not think he understood what she wanted in the letter and "sure enough, when we saw the correction, the correction was incorrect again." Id.

Petitioner later wrote a letter to Dr. Tsai asking him to write about their prior discussion and saying the vaccine caused her problem, but he refused to do that. Id. at 402-03. Petitioner denied the accuracy of Dr. Lin's first correction to the medical records in Exhibit 13 that the onset of her symptoms was August 2012, changing the onset from a few months to two months before petitioner's first visit to Dr. Lin. Id. at 405. Petitioner decided that at the next appointment with Dr. Lin, she would talk to her about when the onset of her symptoms occurred "and say, look, this [first correction Dr. Lin made] is still a problem for me because it throws the timeline all off." Id. at 406. Petitioner continued in discussing her conversation with Dr. Lin:

> --you remember I came to see you right after I had seen Dr. Xu and she had me do the labs and I came in right after. And she [Dr. Lin] said, well, yeah, we've already talked about that. And I said, well, no, the chart still says August and it was changed incorrectly. And she goes, well, what did they put. And she looked back to see what they had put and she was like, oh, that's not what we intended. So I asked her, could you put a note in reflecting this conversation that you realized it was two weeks, not August. . . .

Id. Petitioner said Dr. Lin agreed to change the onset a second time, but "it would reflect badly this many years later," but she said Dr. Lin did remember the conversation. Id. at 406-07.

Petitioner said Dr. Lin "was very upset about Dr. Matloubian's accusations that she was overprescribing medications, that she shouldn't have started me on all these, and she was saying – so she also wrote a letter saying to my husband and I [sic] that if we felt that the medication I was on was too much, that it was not the right medication, that it was not the right diagnosis, she would be more than happy to go over and sit with us and talk about it, that we could have a second referral, go see someone else." Id. at 407.

Dr. Lin offered to take petitioner off Actemra and see if her symptoms came back, but then said she might not be able to put petitioner back on Actemra and petitioner would have to go on steroids, which was unacceptable to petitioner. Id. Dr. Lin suggested petitioner then stay on Actemra and petitioner went for a second opinion. Id. Then, petitioner saw Dr. Lau two

weeks later who said he did not know how much he could help her if she stayed on Actemra. Id. at 408. Dr. Lin said to petitioner that when she first saw petitioner, her lab results were not impressive but her symptoms were. Id. Dr. Lin said it was her symptoms she was treating and petitioner looked better because Actemra was working for her. Id.

Petitioner testified that since Dr. Matloubian suggested that the Kaiser doctors were not the best rheumatologists to see, she went to see Dr. Patel. Id. at 410. Dr. Patel told petitioner that she agreed with Dr. Lin. Id. at 411. Dr. Patel said she was very impressed that Dr. Lin had acted so quickly because it would help to stop the progression of petitioner's disease. Id. at 411-12. Dr. Patel told petitioner that Dr. Lin must have really seen something to move aggressively and do all this. Id. at 412. Petitioner said that Dr. Patel told her Dr. Patel agreed 100 percent with what Dr. Lin did and the time frame in which she did it. Id.

Petitioner testified that a couple of days before she called to make an appointment with Dr. Xu, she was talking to another nurse about her symptoms and petitioner said she thought the flu vaccine had been responsible for the symptoms. Id. at 416. Dr. Lin told petitioner it would be very hard to prove her symptoms came from a flu vaccine. Id. at 417. And then Dr. Lin told her she was going to treat petitioner for the symptoms. Petitioner wanted to see an immunologist because it was the second time she had had a bad reaction after an injection. That was how petitioner got the referral to Dr. Tsai. Id.

After petitioner saw Dr. Tsai in May 2013, she had Kaiser enter into her chart that she was allergic to flu vaccine as well as sulfa. Id. at 418. She said that Dr. Tsai suggested that she never receive flu vaccine again. Petitioner said that Dr. Lin did not suggest one way or the other that flu vaccine had caused her condition. Dr. Lin would say she was worried about petitioner's fingers. Id. When petitioner asked Dr. Lin to get the nailbed test done, Dr. Lin said "we could have done that." Id. at 419. Dr. Lin said she did not doubt that petitioner had Raynaud's phenomenon. Because the capillaroscopy did not have a way to take a photo of the image, she took a photo on her cellphone. But Dr. Lin said petitioner did not even need a photo. All she had to do was look at her nailbeds and see if under them, she had redness. Dr. Lin said that redness is a sign of all the dead capillaries there. Id.

On redirect examination, petitioner said that she did not have a manicure prior to the nailfold capillaroscopy test. Id. at 430. Petitioner also said she does not bite her nails or play the guitar. Id. at 431.

Medical Expert Reports filed after the hearing

On September 8, 2017, petitioner filed Dr. Ahmed's rebuttal. Ex. 103. Dr. Ahmed states that petitioner's pre-2012 flu vaccination health concerns were not autoimmune and should be considered separately from her new symptoms, diagnoses, and laboratory abnormalities post-2012 flu vaccination. Id. at 1. He also provides an Appendix to document this point as well as a graphic representation of petitioner's symptoms and their onset post-vaccination in 2012 (Ex. 104). Dr. Ahmed focuses on a statement in Ex. A, Tab 2, at 6 (the Kasukawa criteria for

MCTD), which states that the titer of the anti-RNP does not need to be high to qualify someone for a diagnosis of MCTD. Ex. 103, at 1. This same point is in Ex. A, Tab 3, at 1, and in Ex. 105. Id. at 1-2. Thus, Dr. Ahmed states that petitioner's ANA of 1:320 titer and anti-RNP antibodies of 1.2 are compatible with MCTD post-2012 flu vaccination. Id. at 2. He also refers to Exhibit 105 from the Mayo Clinic ("Connective Tissue Disease Cascade") which notes that RNP antibodies ≤1.0 are considered positive results and support the diagnosis of MCTD. Id.

Dr. Ahmed answers Dr. Matloubian's point that petitioner's CRP's slight elevation of 0.7 was insufficient to denote MCTD. Dr. Ahmed states that anemia of chronic disease, high platelets, and very elevated levels of ESR/CRP might not have developed because petitioner took NSAIDS, steroids, and potent immunosuppressives, such as MTX, etanercept, abatacept, and Actemra (tocilizumab). Id. To Dr. Ahmed, that petitioner's CRP was slightly elevated in the context of these anti-inflammatory treatments means she had significant inflammation which is consistent with MCTD. Id. As for petitioner not having myositis, elevated creatine kinase, aldolase, or elevated liver function tests, Dr. Ahmed states that in the Alarcón-Segovia criteria in Ex. A, Table 2, at 6, myalgias can be substituted for myositis. That means muscle pain (which petitioner had) can substitute for muscle inflammation. Id.

Dr. Ahmed focuses on Dr. Matloubian's statement that petitioner has something but he does not know what it is as an apparent agreement that petitioner developed some disease after flu vaccination. Id. Dr. Ahmed notes that petitioner's various medications could have impacted the results of examinations and tests at different times. He states he agrees with the findings of petitioner's Dr. Xu, Dr. Lin, Dr. Lau, and Dr. Patel that she had evolving features consistent with MCTD: positive RNP antibodies, synovitis, and afterward, puffiness of fingers, myalgias, thickening of skin, and Raynaud's disease. All of petitioner's treating doctors agree she had an unfolding autoimmune disease after her September 20, 2012 vaccination. Id.

Dr. Ahmed defends the concept of molecular mimicry by referring to Ex. A, Tab 1, at respondent's page 14[100] and petitioner's exhibit 79.[101] Id. at 4. He reiterates that petitioner's blood sample showing a homogeneous pattern of ANA could have masked a speckled pattern. Id. Dr. Ahmed agrees with Dr. Matloubian that petitioner's chronic pain syndrome is unrelated to symptoms of MCTD. Id. Dr. Ahmed disagrees with Dr. Matloubian's opinion that petitioner has autoimmune thyroid disease since she does not have thyroid peroxidase antibodies. Id. at 5. Therefore, Dr. Ahmed concludes that petitioner did not have a pre-existing autoimmune disease before she received flu vaccine on September 20, 2012. Id.

On October 12, 2017, respondent filed Dr. Matloubian's response to Dr. Ahmed's rebuttal (Ex. 103). Ex. F. He criticizes Dr. Ahmed's Appendix, attached to his rebuttal at page

[100] Robert M. Bennett, Anti-U1 RNP antibodies in mixed connective tissue disease, UPTODATE, http://www.uptodate.com/contents/anti-u1-rnp-antibodies-in-mixed-connective-tissue-disease (last visited September 11, 2018).

[101] Hans H. Guldner et al., Human Anti-P68 Autoantibodies Recognize a Common Epitope of U1 RNA Containing Small Nuclear Ribonucleoprotein and Influenza B Virus, 171 J EXPERIMENTAL MED 3:819-29 (1990). The authors describe a subset of human autoantibodies that react against a protein in influenza B viruses. Id. at 820.

6, which Dr. Ahmed divided into petitioner's symptoms prior to and after her September 20, 2012 flu vaccination. Dr. Matloubian states that Dr. Ahmed omitted petitioner's pre-vaccination history of hand pain which is important because petitioner's hand pain prompted her personal care physician to order an ANA test on March 3, 2008 to rule out autoimmune disease. Id. at 1. A rheumatologist thought petitioner did not have an autoimmune disease because of her hand pain. Id. Dr. Matloubian also notes that Dr. Xu on October 3, 2012 had never documented a physical examination of petitioner's hands before the vaccination at issue in this case. Therefore, Dr. Xu was in no position to determine if petitioner's hand swelling was new when she noted on October 3, 2012 that petitioner had new swelling. Dr. Matloubian also criticizes Dr. Ahmed for omitting in his Appendix that petitioner on the October 3, 2012 visit was still having pain in her joints, knees, hands, and lower back, but her shoulder was improving. Id. To Dr. Matloubian, petitioner manifested the same symptoms post-vaccination as pre-vaccination. Id. at 2.

Dr. Matloubian also emphasizes that Dr. Ahmed failed to point out that when petitioner took blood tests on October 3, 2012, she was not on any anti-inflammatory drugs including NSAIDS, yet her CRP test was normal even though she had symptoms. Id. Dr. Matloubian says that even when petitioner had symptoms within weeks of her flu vaccination on September 20, 2012, she did not have evidence of a systemic inflammatory disease because of the negative inflammatory markers. Id. Dr. Matloubian takes issue with Dr. Ahmed's statement that petitioner's taking NSAIDs explains the negative inflammatory markers when she complained of joint pain. Id. Dr. Matloubian states that NSAIDs do not remedy joint inflammation and elevated inflammatory markers in patients with RA and MCTD. If they did, the doctors would not give stronger medication to these patients. When this type of patient is tested in clinical trials of new anti-inflammatory drugs, the patient is allowed to stay on NSAIDSs because they do not alter the results of the tested anti-inflammatory drugs. Id. He concludes that petitioner's failure to have any elevated inflammatory markers although she had joint swelling is highly unlikely to be attributable to her taking NSAIDs. Id.

Dr. Matloubian criticizes Dr. Ahmed for omitting from his Appendix the fact that Dr. Lin during the October 31, 2012 visit noted petitioner for many months had symptoms of symmetrical pains of both hands, knees, and toes, associated with prolonged morning stiffness. Id. When petitioner asked her to change that length of time to weeks, Dr. Lin wrote petitioner had all those symptoms for two months, i.e., since August 2012. Dr. Matloubian emphasizes the onset of petitioner's symptoms occurred prior to her September 20, 2012 flu vaccination. Id. He notes Dr. Ahmed does not believe the onset of her condition occurred before this vaccination and, thus, denies the vaccination significantly aggravated her condition.

Dr. Matloubian states that Dr. Lin on March 4, 2013 noted swelling only of petitioner's left knee which she attributed to Baker's cyst, a non-rheumatologic condition, but did not document any synovitis or skin thickening or any limitation of petitioner's range of motion of joints. Id. He agrees however with Dr. Ahmed that Dr. Lin noted for the first time on August 19, 2013 that petitioner had synovitis of one small joint of her left hand. Id. Dr. Matloubian writes that Dr. Lin's note of January 6, 2014 that petitioner always complained of joint pains of her PIPs and MCPs and wrists, but Dr. Lin did note synovitis on physical examination that day

as proof that Dr. Lin did not find any objective evidence that petitioner had an ongoing autoimmune process affecting the small joints of her hands, despite petitioner's complaint of symptoms. Id. at 3. Dr. Matloubian states that since petitioner did not take an anti-RNP test before her flu vaccination on September 20, 2012, Dr. Ahmed cannot say petitioner allegedly developed this antibody only after the vaccination and due to the vaccination. Id.

Dr. Matloubian emphasizes the importance of a positive anti-RNP as diagnostic of MCTD. He states petitioner had several test results that were discordant, including a homogeneous ANA result and a negative Smith+RNP result. The RNP antigen is part of Smith+RNP. Thus, Dr. Matloubian states it is highly unusual to have a positive anti-RNP antibody test while having a negative anti-Smith+RNP result. Id.

Dr. Matloubian states petitioner does not satisfy the four proposed criteria in Table 1 of Ex. A, Tab 2, page 6, for diagnosing MCTD. Dr. Matloubian says in his experience, he has not seen one patient with MCTD who failed to have any abnormal physical examination findings or negative laboratory values who was only on NSAIDs. He finds it quite unlikely that petitioner's NSAIDs caused her lack of objective findings when she first presented to Dr. Lin. Id.

Dr. Matloubian takes further exception to petitioner's having a diagnosis of MCTD because she never had significant abnormal lab values indicative of chronic inflammation at any time. Id. She had one determination of ESR, which was normal on March 3, 2008, after she complained of hand pain. Before her vaccination, she was not tested for abnormal CRP levels. After her September 20, 2012 flu vaccination, and before she took any drug, she had a normal CRP test on October 3, 2012 when she complained of symptoms. He concludes that she did not have any signs of systemic inflammation that a doctor could attribute to her vaccination when she saw her doctor on October 3, 2012. Dr. Matloubian cites Dr. Ahmed stating during the hearing that CRP responds rapidly to a stimulus and indicates inflammation. Dr. Matloubian finds however that ESR better indicates chronic inflammation and petitioner had normal ESR on October 31, 2012. She had a mildly abnormal CRP only once on May 14, 2013 when it had a value of 0.7 (normal is less than 0.5). Id. Dr. Ahmed attributed this slight elevation in CRP to the vaccination which was eight months earlier. Id. at 3-4. Dr. Matloubian states that he sees in his rheumatologic practice CRP values that are 20-100 times higher than baseline in patients with chronic inflammatory arthritis. Id. at 4.

Dr. Matloubian notes that petitioner did not have myositis when she saw Dr. Lin on October 3, 2012. The tests of her creatine kinase, aldolase, and liver function did not show elevation. In addition, Dr. Lin found she had normal muscle strength. Petitioner never developed myositis. Dr. Matloubian doubts she ever had inflammatory myositis. She did however complain of myalgias or muscles aches when she saw Dr. Lin on October 3, 2012. Even though Dr. Ahmed wrote that myalgia could substitute for myositis in the diagnosis of MCTD, Dr. Matloubian states that myalgia is only one of the Alarcón-Segovia criteria. Petitioner did not have high-titer anti-RNP, swollen hands, synovitis, Raynaud's phenomenon, or acrosclerosis. Therefore, Dr. Matloubian states that petitioner did not meet the Alarcón-Segovia criteria for diagnosis of MCTD on October 3, 2012, even if she had had a high-titer anti-RNP

antibody, which she did not. Id.

Dr. Matloubian notes that Dr. Lin and Dr. Lau examined petitioner within one week of each other yet documented different physical examination findings. Dr. Lau seemed not to be confident of the diagnosis of MCTD because he considered additional serologic workup with 14-3-3-ETA for supporting a diagnosis of rheumatoid arthritis and anti-RNA polymerase III for supporting a diagnosis of SSc. Dr. Lau also pondered if petitioner had possible UCTD because she did not meet the criteria for diagnosing a specific CTD. Dr. Patel pondered petitioner's having a seronegative RA and thought the only way to determine if she had RA was for her to stop taking Actemra. Id. The three rheumatologists could not agree whether or not petitioner had sclerodactyly or synovitis. Dr. Matloubian explains that the puffiness of fingers and sclerodactyly seen in some rheumatologic diseases occurs because of deposition of collagen in tissues underlying the skin. Id. In a trial of Actemra to treat scleroderma, it took almost a year for an insignificant difference to be seen in skin that was treated. Id. Because these three rheumatologists disagree on the significance of what they saw, Dr. Matloubian said it is quite difficult to make a diagnosis based on the medical records. Id. at 5.

Regarding the flu vaccination of September 20, 2012 as causative, Dr. Matloubian states Dr. Lin recorded petitioner's symptoms began in August 2012, before her vaccination. When petitioner saw Dr. Xu on October 3, 2012, and was not on any treatment, she did not manifest systemic inflammation and had no new complaints but was complaining about the symptoms she had before vaccination. These facts persuade Dr. Matloubian that petitioner's flu vaccination was not the cause of her condition. He notes that petitioner's Raynaud's phenomenon was first documented on November 19, 2014, more than two years after her September 20, 2012 flu vaccination. He adds that at that time, petitioner was receiving Enbrel which paradoxically leads to development of autoimmune diseases. Dr. Matloubian writes, "Drug-induced MCTD is a rare occurrence but may be an occasional feature of anti-tumor necrosis factor (TNF) therapy." Ex. A, Tab 4, at 1. Dr. Ahmed identified Dr. Bennett as a leader in the MCTD field. Petitioner was being treated with Enbrel in 2013, and Enbrel is an anti-TNF drug. Dr. Lin thought Enbrel had caused petitioner to develop a malar rash and told her stop taking Enbrel. Dr. Matloubian thus states he cannot completely rule out the fact that petitioner's drugs contributed to her current condition and development of a possible autoimmune disease. Id.

Dr. Matloubian discusses the capillaroscopy photographs that constitute Exhibit 94. He showed them to the director of the UCSF Scleroderma Center, and told the director that six years previously, petitioner was diagnosed with MCTD and had an ANA of 1:320 with a homogeneous pattern, and an RNP of 1.2 by multiplex assay, but no other autoantibodies. The director of the UCSF Scleroderma Center who had previously seen scleroderma patients also at Johns Hopkins said he could not interpret the photos. He mentioned artifacts could occur due to manicures. Dr. Matloubian attached as Tab 1 to his report an article[102] that notes, "Some habits such as manicures, onychophagia, and guitar playing cause microhemorrhages, which obviously do not

[102] Satoshi Kubo and Yoshiya Tanaka, Usefulness of nailfold videocapillaroscopy for systemic sclerosis, INFLAMMATION AND REGENERATION 36:5 (2016), https://inflammregen.biomedcentral.com/articles/10.1186/s41232-016-0001-x (last visited September 13, 2018).

depend on any pathological condition. Hence, patients should remove nail polish 2 weeks before the examination." Ex. F, Tab 1, at 3.

Dr. Matloubian criticizes Dr. Ahmed's attribution of the increase in the titer of petitioner's ANA from 1:160 in 2008 to 1:320 in 2012 to her receipt of flu vaccine on September 20, 2012. Id. Dr. Matloubian says that the difference between 1:160 and 1:320 is only one dilution and quite insignificant particularly because two different labs performed the test. Id. at 6. He notes Dr. Ahmed provided multiple papers indicating this change in ANA is not clinically significant. The change does not indicate either disease severity or development of new or worsening autoimmunity. Fluctuations in ANA titers do not necessarily correlate with disease activity. Dr. Ahmed states that changes in anti-dsDNA can be reflected in ANA titer, but Dr. Matloubian counters that petitioner never tested positive for anti-dsDNA. Id. He also mentions that anti-RNP antibodies also do not fluctuate with disease activity. Id.

He reiterates that Dr. Ahmed's attribution to Raynaud's of numbness in the bottom of petitioner's feet had nothing to do with Raynaud's. Raynaud's involves spasms of the digital arteries, not the palmar/plantar arteries. Exhibit 19 consisting of photos of petitioner's fingers showed pink fingers, not white or dusky ones. Id.

Dr. Matloubian questions Dr. Ahmed's reliance on the theory of molecular mimicry to explain how flu vaccine can cause MCTD. Id. Dr. Matloubian says the etiology of MCTD is unknown. Id. at 7. In addition, as Dr. Ahmed testified, anti-RNP is not thought to cause disease. Dr. Ahmed further testified that someone having anti-RNP antibodies is not necessary for having MCTD. Thus, to Dr. Matloubian, even if molecular mimicry antibodies to flu virus could cross-react with RNP, i.e. be anti-RNP antibodies, is irrelevant since anti-RNP antibodies do not cause MCTD. Id. In addition, Dr. Matloubian found errors in the medical articles which Dr. Ahmed cited supposedly proving an association between several viruses and MCTD. Id. at 6. Specifically influenza B virus is not a murine retrovirus and does not contain a "GAG" antigen (referring to Ex. 67, at 9). Id. at 6-7. Both petitioner's exhibit 66 and respondent's exhibit A, Tab 1, make the same error. Id. at 7. Dr. Matloubian also faults exhibit 79 because of methodological flaws leading to antibody cross-reactivity having no biological significance. Id.

Dr. Matloubian states that the results of petitioner's anti-RNP and Smith-RNP test are internally inconsistent. Id. at 8. The first was positive while the latter was negative. Yet if the first result were accurate, they would both be positive. The same antigen present in RNP beads is present in Smith-RNP beads ("smRNP"). If petitioner really had a positive anti-RNP test, she should also have had a positive anti-Smith+RNP test. The beads used for this type of assay can non-specifically bind to antibodies found in serum, giving a low false positive result. Dr. Ahmed did not discuss this discrepancy. Id.

As for onset of petitioner's chronic pain syndrome, Dr. Matloubian notes that Dr. Lin wrote that it began several months earlier and specifically in August 2012, which is before her September 20, 2012 flu vaccination. Id.

Dr. Matloubian recounts Dr. Ahmed's testimony about his publication of articles linking autoimmune diseases to vaccination. Id. at 9. Specifically, exhibit 57 states there are no biomarkers helping investigators determine who will develop an autoimmune disease after vaccination. This, to Dr. Matloubian, means that petitioner's positive ANA is irrelevant because it is not predictive of autoimmune disease. It also defeats Dr. Ahmed's thesis that subsequent flu vaccinations "boosted" petitioner's ANA response. Id.

Dr. Matloubian notes that it is unclear whether petitioner's symptoms changed after flu vaccination. Dr. Xu and Dr. Lin agree that her musculoskeletal symptoms existed before her September 20, 2012 flu vaccination and they did not record any significant changes after that immunization. Id. Moreover, no one tested petitioner before flu vaccination on September 20, 2012 for anti-RNP antibodies. Exhibit 28 shows that these autoantibodies can be present years before autoimmune disease reaches a clinical stage. None of petitioner's medical articles substantiate that flu vaccine causes anti-RNP antibodies to develop. Id.

Dr. Matloubian believes that petitioner's hypothyroidism is likely due to autoimmune thyroid disease, suggesting petitioner had pre-existing autoimmune disease. Petitioner's mother also has autoimmune thyroid disease (Hashimoto's thyroiditis). Dr. Matloubian thinks petitioner having autoimmune thyroid disease explains her positive ANA with a homogeneous pattern. Id. Dr. Ahmed, on the other hand, denies that petitioner had pre-existing autoimmune thyroid disease because her anti-thyroid peroxidase antibodies were negative. An article respondent filed as Tab 2 to Dr. Matloubian's report (Ex. F) notes that although 90 percent of patients with hypothyroidism have elevated antibodies to thyroid peroxidase, 10 percent do not. Id. He states that Dr. Ahmed dismissed the fact that a high-titer anti-RNP antibody is essential in MCTD and present in 95-100 percent of patients (Ex. 89). He dismissed this requirement with the statement that an individual can have MCTD without having a positive anti-RNP. Id. at 9-10. Yet, when analyzing whether or not petitioner has autoimmune thyroiditis, Dr. Ahmed insists anti-thyroid peroxidase antibodies are diagnostic, when the literature shows 10 percent do not have them. Id. at 10.

Dr. Matloubian notes that Dr. Ahmed gave three separate explanations for petitioner's pre-existing positive ANA: (1) her prior flu vaccination primed her and her subsequent flu vaccination boosted her; (2) her positive ANA could be the ANA seen in 10 to 20 percent of the normal population and can be in a homogeneous pattern; and (3) during the hearing, Dr. Ahmed said that petitioner's ANA pattern which was homogeneous contrasts with the ANA pattern for 60-70% of people with autoimmune thyroid disease which is speckled. However, Dr. Matloubian states that ANA speckled pattern is not associated with autoimmune thyroid disease. He says that exhibit A, Table 7, states ANA with a homogeneous pattern is associated with Hashimoto's thyroiditis. Id.

Dr. Matloubian concludes that he cannot make a definitive diagnosis of petitioner having a rheumatologic disease when her three treating rheumatologists cannot agree on a diagnosis and used different signs and symptoms to reach a diagnosis. Moreover, petitioner's musculoskeletal symptoms occurred before her September 20, 2012 flu vaccination. Her medical records do not

note any changes in quality or distribution of her musculoskeletal symptoms within a short time of her vaccination. Weeks later, when she was not on anti-inflammatory medications, her tests for systemic inflammation were normal. Years later, two of her rheumatologists considered discontinuing Actemra and/or performing additional blood tests to look for physical and laboratory evidence of systemic inflammation. Id. In addition, Dr. Patel did not have access to all of petitioner's medical records, as apparent in the filing of exhibit 104, at 4.

Dr. Matloubian finds Dr. Ahmed's theory of causation not plausible. Id. Although anti-RNP is a major feature of MCTD, anti-RNP does not cause MCTD. Id. at 10-11. Thus, any theory of molecular mimicry between flu vaccine and RNP is irrelevant. Id. at 11. Lastly, changes in ANA titer are not reflected in clinical symptoms. Id.

On November 20, 2017, petitioner filed Dr. Ahmed's sur-rebuttal statement. Ex. 110. Dr. Ahmed states that he omitted petitioner's history of prior hand pain because hand pain is non-specific and does not necessarily reflect arthritis, noting osteoarthritis is not autoimmune. Id. at 1. The rheumatologist whom petitioner saw in referral did not think her hand pain was autoimmune. Id. Dr. Ahmed thinks that Dr. Xu did not document pre-vaccination hand swelling because in prior visits, petitioner's hands were not abnormal. Id. at 2. To Dr. Ahmed, pain does not qualify as an autoimmune disease and is not usually due to autoimmune disorder. Id.

Dr. Ahmed states that CRP is not always elevated in inflammation associated with autoimmune disease. He says that MCTD has components of polymyositis, scleroderma, and systemic lupus erythematosus. He notes that with lupus, a patient may have a normal CRP while having significant tissue damage and inflammation. When petitioner received flu vaccine on September 20, 2012, no one measured her ESR. Only her CRP was measured. Dr. Ahmed says the normal result on her CRP test may have been due to high levels of type 1 interferons that inhibit CRP production in hepatocytes (liver cells). Id.

Dr. Ahmed disagrees with Dr. Matloubian over the effectiveness of NSAIDS to reduce systemic inflammation, but notes patients cannot use them over a long period because of side effects. Id. at 3.

Dr. Ahmed bases his causation opinion on the onset of petitioner's symptoms occurring weeks after her flu vaccination rather than months before because of the "correction" petitioner persuaded Dr. Lin to write in her medical records on January 5, 2016.

(This was the second "correction" Dr. Lin made at petitioner's request, the first one being on June 19, 2015 when Dr. Lin changed onset of "many months" earlier to "two months" earlier, putting onset in August 2012, still before the September 20, 2012 flu vaccination. Thus, Dr. Ahmed picked the only one of these two "corrections" that would put onset of petitioner's symptoms after the flu vaccination, in effect removing petitioner's alternate allegation of significant aggravation which she included in her amended petition. Dr. Ahmed's language to describe the change of onset from the original "many months" earlier than October 31, 2012 to "two months or August 2012" to "weeks" is curious. He uses the phraseology **"it was not until**

the second attempt on January 5, 2016 that the records finally reflected Dr. Lin's correction [emphasis added].**"** Id. The records do not have a mind of their own, failing to reflect petitioner's repeated attempts to change them. The only reason the date of onset in the records changed was petitioner twice requested Dr. Lin to change them. The changes were not Dr. Lin's attempts to get onset "right" after three tries on October 31, 2012, June 19, 2015, and January 5, 2016. These onset changes were certainly not a "final reflection" of Dr. Lin's mind. It is ludicrous of Dr. Ahmed to insinuate that Dr. Lin, over three years and two months after she wrote an initial history on October 31, 2012 of onset months before the September 20, 2012 flu vaccination, finally wrote an onset date that reflected her mind rather than petitioner's mind.)

Dr. Ahmed concludes regarding onset in his sur-rebuttal that the onset of petitioner's autoimmune symptoms was not prior to her September 20, 2012 immunization. Id. But, he says, "Even if this error in the medical records was not corrected," it still does not suggest petitioner had pre-existing autoimmune disease because her pre-vaccination pain does not mean she had an autoimmune disease. Id. Moreover, the medical records do not support petitioner had swelling and inflammation for many months pre-vaccination. Id.

He disagrees with Dr. Matloubian's statement that petitioner's Baker's cyst behind her left knee, which Dr. Lin noted on March 4, 2013, was petitioner's only swelling and therefore not rheumatologic. She did not have synovitis or skin thickening and her range of motion was not limited. Dr. Ahmed writes that Baker's cysts can be due to RA. Id. (Petitioner has never been diagnosed with RA.)

Dr. Ahmed explains the failure of Dr. Lin's finding any synovitis when petitioner saw her on January 6, 2014 to petitioner's taking NSAIDS. Id. at 3-4. Dr. Ahmed says petitioner's anti-RNP was positive and petitioner had evolving features consistent with a diagnosis of MCTD: positive RNP antibodies, synovitis, subsequent puffiness of fingers, myalgias, thickening of skin, and Raynaud's phenomenon, fulfilling the criteria for MCTD. Id. at 4.

Regarding Dr. Matloubian's conclusion that petitioner never had inflammatory myositis, although she did have muscle aches (myalgia) when she saw Dr. Lin on October 3, 2012, Dr. Ahmed again counters that the Alarcón-Segovia criteria for MCTD (Ex. A, Tab. 2, at 6) says myalgias can be substituted for myositis, and muscle pain can be substituted for muscle inflammation (Ex. A, Tab 1, at 10). Id. at 6.

The Alarcón-Segovia criteria in the chart in Ex. A, Tab 2, at 6, say, "Serological criteria plus at least three clinical criteria [edema in hands, synovitis, myositis, Raynaud's phenomenon, acrosclerosis], included either **synovitis or myositis** [emphasis added]." Myalgia is not listed in this chart as a substitute for myositis. Synovitis is an alternative for myositis. Synovitis is "inflammation of a synovium; it is usually painful, particularly on motion, and is characterized by a fluctuating swelling due to effusion within a synovial sac."[103] Myalgia is "pain in a muscle or muscles."[104] Dr. Ahmed agrees that petitioner did not meet the Alarcón-Segovia criteria

[103] Dorland's at 1856.
[104] Dorland's at 1214.

immediately, but states she did meet the criteria as the disease evolved. Of note, in a chart that constitutes part of Ex. A, Tab 1, at 10, is a chart originally from Robert M. Bennett, Overlap Syndromes, in Kelley's Textbook of Rheumatology (8th ed. 2009), which states that myalgia is commonly substituted for myositis.

Dr. Ahmed further disagrees with Dr. Matloubian about petitioner's diagnosis, preferring to rely on her treating rheumatologists even though their physical examination results differed. Id. at 7. He states as his basis that petitioner had pain only before flu vaccination, but post-vaccination she had inflammation (swelling). Therefore, her MCTD started after vaccination. Id. at 7.

Dr. Ahmed does not trust what the director of the UCSF Scleroderma Center told Dr. Matloubian about petitioner's capillaroscopy photographs because Dr. Matloubian's summary "cannot be validated." Id. He also says he cannot validate what information Dr. Matloubian provided this director. Id. Dr. Ahmed says he has seen 100 patients with MCTD, 1,000 patients with scleroderma, and numerous patients with SLE. Id. at 8. He attaches 31 pages of new images of nailfold capillaroscopy (Ex. 109). He emphasizes image 43 (Ex. 109, at 14). He states the close-ups in images 48, 49, and 51 (Ex. 109, at 19, 20, and 22) show in greater detail the nailfold capillaries and the tortuosity in various capillaries, with a red bushy appearance, irregular areas of capillary dropout with unequal white spaces between tortuous capillaries, and only a few hair-like normal capillaries. Id. Petitioner has not undergone finger manicures to explain these appearances. Id.

Dr. Ahmed disagrees with Dr. Matloubian over the relevancy of petitioner's increase in ANA titer. Id. at 9. He states that since anti-dsDNA fluctuates with disease activity, the ANA pattern due to those antibodies has to fluctuate. In SLE, dsDNA is believed to form immune complexes deposited in the kidney. Id.

Dr. Ahmed explains that his reference in a prior report to numbness in the bottom of petitioner's feet was due to Raynaud's phenomenon by stating he was referring to petitioner's toes when he wrote "bottom of her feet." Id.

Dr. Ahmed refers to the Guldner paper (Ex. 79) for positing that influenza B viruses could trigger development of autoantibodies to p68. Id. at 11. He states that while anti-RNP is not considered to cause disease, mimicry with it can generate epitope spreading. Id. Thus, an autoimmune reaction against a particular peptide can spread to other peptides that have some similarity to the initial peptide and cause disease. Id.

Regarding the inconsistent results of a positive anti-RNP test and a negative Smith+RNP test, Dr. Ahmed says petitioner's findings are consistent with Ex. A, Table 4, at 118, where, using the same technology, only 15/16 patients with a diagnosis of MCTD were positive for both RNP and SM+RNP.[105] Id. at 13. He interprets this to mean one out of 16 patients with MCTD

[105] Dr. Ahmed did not provide the reference or tab number, making a search for this article among 25 articles respondent filed together with Exhibit A difficult. There is an article that is reference or tab 9 to Exhibit A (Moder),

did not have positivity to both Smith+RNP and RNO. Then he says, "it is not unexpected that [petitioner] was positive for RNP, but not for Smith+RNP." Id.

He denies that petitioner had swelling and inflammation prior to her September 20, 2012 flu vaccination, relying on Dr. Lin's second correction of her initial October 31, 2012 record on January 5, 2016. Id. He says petitioner's symptom pre-vaccination was pain and post-vaccination was inflammation. Id. at 14.

Dr. Ahmed states high titers of RNP antibody are not required to diagnose MCTD although they are relevant for a specific subset of patients with MCTD. Id. at 15. He states that primary thyroid disease does not indicate only autoimmune thyroiditis but includes other non-autoimmune diseases that damage the thyroid. Id. at 16. People who do not have autoimmune causes of primary thyroid disease do not have anti-TPO antibodies. To Dr. Ahmed, the absence of TPO antibodies makes it more likely that petitioner's primary thyroid disease has a non-autoimmune cause. Id. He refers to the Guldner article (Ex. 79) as proof that petitioner received the flu vaccine that is in the article, even though petitioner received B/Wisconsin/1/2010-like virus (Yamagata lineage), not B/Beijing/1/87 as in the article. The article states that B/Beijing/1/87 can generate antibodies that cross-react with the major autoantigen for MCTD. Dr. Ahmed thinks the Guldner article supports flu vaccine generates ANA.

He says that he and Dr. Matloubian agreed at the hearing that a homogeneous pattern of ANA can hide a speckled pattern. Id. Dr. Ahmed agrees that a homogeneous pattern of ANA may be specific for Hashimoto's thyroiditis, but may be seen with other diseases. Id. at 17. He concludes that changes in ANA titer can be clinically relevant as occurs in lupus in which the dsDNA antibodies fluctuate and correlate with kidney disease activity. Id. at 18.

On February 15, 2018, respondent filed Dr. Matloubian's response to Dr. Ahmed's sur-rebuttal statement (Ex. 110). Ex. G. Regarding petitioner's two-fold change in her ANA titer from 1:160 in 2008 to 1:320 in 2012, Dr. Matloubian writes that both Dr. Ahmed and he agree that reading ANA titers can be subjective and a two-fold difference is not medically significant. Id. at 1. Secondly, the positive anti-U1-RNP test could be a false positive since in the same assay, the anti-U1-RNP and Smith portion of the test (another way of measuring anti-U1-RNP antibodies) was negative. Id. An article petitioner filed as Ex. 72 (Satoh)[106] states the titer of

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which at Table 4 shows that of 16 MCTD individuals tested, 16 out of 16 or 100 percent had agreement between two methods of antibody testing (Multiplex immunoassay and EIA or enzyme immunoassay) for positivity for ANA, 15 out of 15 or 100 percent for antibodies to SmRNP, and 14 out of 15 or 93 percent for antibodies to RNP. That is at page 982, not 118 of the article. There is no article that the undersigned can find among the 25 respondent filed that has the page 118. The authors conclude that overall agreement between the methods of testing (Multiplex and EIA) was 100 percent for ANA and SmRNP, but 94 percent for RNP. This does not mean individuals with MCTD were less likely to be positive for RNP. It means the two types of testing for antibodies were not in complete agreement in detecting antibody presence. The undersigned points out that Exhibit A, Tab 8, Table 1, internal page 140 (De Beéck), shows that individuals with MCTD tested with BioPlex 2200 for reactivity to specific antigens were 100 percent positive for both RNP and SmRNP.

[106] Minoru Satoh et al., Clinical interpretation of antinuclear antibody tests in systemic rheumatic diseases, 19 MOD RHEUMATOL 3:219-28 (2009). Satoh states "it should be noted that higher titers of ANA do not always mean that the patient's disease is more severe or active." Id. at 3. He notes that anti-U1RNP autoantibodies are associated

anti-U1-RNP does not correlate with disease activity in MCTD. Thus even if the positive anti-U1-RNP were not a false positive, the rise in titer is irrelevant to the disease process. Id.

Dr. Matloubian agrees with Dr. Ahmed that anti-dsDNA may fluctuate with disease activity in lupus patients who are anti-dsDNA positive, but this is not true for other autoantibodies. Id. at 2. He notes that petitioner was tested for anti-dsDNA antibodies and the result was negative, making Dr. Ahmed's argument regarding changes in the ANA titer as a marker of disease activity irrelevant in this case. Id.

Dr. Matloubian notes that on the two occasions in which petitioner's ANA was tested, her ANA pattern was homogeneous, a result inconsistent with a diagnosis of MCTD for which one needs a high titer (>1,000) ANA with a speckled pattern. Id. He thinks her positive ANA was due to her having autoimmune thyroid disease. Dr. Ahmed believes that petitioner's ANA did have a speckled pattern but the homogeneous pattern hid it. Id.

Dr. Matloubian takes issue with Dr. Ahmed's concept of epitope spreading in which an autoimmune reaction against a particular peptide spreads to other peptides that have some similarity to the initial peptide. Id. Dr. Matloubian says that epitope spreading requires an infection or autoimmunity to start tissue damage. Id. at 3. Dr. Ahmed used the concept of epitope spreading with anti-U1-RNP antibodies, but then conceded that these autoantibodies do not cause tissue damage and the disease manifestation seen in MCTD. Id. at 2.

Dr. Matloubian questions Dr. Ahmed's opinion on onset. Id. at 3. Dr. Matloubian finds it clear that petitioner's pre-existing musculoskeletal symptoms did not change after her September 20, 2012 flu vaccination. Dr. Xu, her PCP, noted on October 3, 2012, two weeks post-vaccination, that petitioner was still having pain in her joints, knees, hands, and lower back, but her shoulder pain was improving. Id. Dr. Matloubian writes that if petitioner were having a systemic autoimmune disease that affected her joints because of the flu vaccination, her shoulder improvement should not have happened. Id. at 3-4. In addition, on October 3, 2012, petitioner's CRP, an inflammatory marker, was normal (Med. recs. Ex. 3, at 40-41). Dr. Ahmed testified at the hearing that CRP rises rapidly in response to inflammation. Id. at 4. When petitioner was tested on October 3, 2012, she was not on any NSAIDS or other treatments that would have affected her CRP test result. Dr. Matloubian concludes that as of October 3, 2012, she did not have any evidence of a systemic inflammatory disease as a result of her September 20, 2012 flu vaccination. Id. However, her anti-RNP on October 3, 2012 was abnormal, being slightly elevated at 1.2 when normal is less than 1.0. Although Dr. Matloubian considers this result a false positive, even if it were correct, this autoantibody is not connected to flu vaccine. He states that Dr. Ahmed has conceded that this autoantibody does not cause disease and therefore cannot cause tissue damage. Id. Moreover, Dr. Matloubian thinks it probable that petitioner had anti-RNP antibodies for many years before she received flu vaccine on September 20, 2012. Id.

Dr. Matloubian notes that Dr. Lin's first notation of history on October 31, 2012 reflected

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with Raynaud's phenomenon, swollen hands, leukopenia, and overlapping features such as sclerodactyly or myositis. Id. at 4.

that petitioner had musculoskeletal symptoms for many months (Ex. 3, at 48). She also noted petitioner had myalgias which she also had in the past. But petitioner asked Dr. Lin to change the onset in her initial record from many months before October 31, 2012 to "several weeks (Ex. 10, at 1), but Dr. Lin instead changed her October 31, 2012 history from "many months" to "two months" starting in August 2012, which was still before her September 20, 2012 flu vaccination. Petitioner made a third go at having Dr. Lin change the October 31, 2012 notation of onset via another letter after petitioner had done "research" on her vaccine claim (Ex. 112). This time, Dr. Lin changed the onset of petitioner's symptoms to four weeks since the end of September 2012, i.e., post-vaccination. Id.

Dr. Matloubian emphasizes that Dr. Lin's first evaluation of petitioner on October 31, 2012 did not reveal any evidence of inflammation in petitioner's joints or any evidence of skin changes supportive of a diagnosis of MCTD. Id. Petitioner's blood tests for inflammatory markers, i.e., ESR and CRP, were normal. Dr. Matloubian states:

> As a practicing rheumatologist, I have a great deal of experience in treating patients with inflammatory arthritis, as the petitioner has been alleged to have. Even though patients with a true autoimmune arthritis, such as rheumatoid arthritis or MCTD, may receive slight symptomatic relief from NSAIDS, their inflammatory markers such as ESR and CRP, do not normalize. That's why additional medications, such as methotrexate and biologics, are used to bring down the inflammation and normalize laboratory values. … The petitioner did not have elevated inflammatory markers at presentation when she was not taking any medication. . . .

Id.

Dr. Matloubian says that Dr. Ahmed conceded at the hearing that he would not have treated petitioner for MCTD on October 31, 2012 based on Dr. Lin's documentation. Id. at 5.

Dr. Matloubian notes that two other rheumatologists, Dr. Lau and Dr. Patel, appear not to have had petitioner's full records when they evaluated petitioner. Moreover, they documented different physical examination findings. Dr. Matloubian says many of petitioner's symptoms that Dr. Lau attributed to connective tissue disease pre-existed her September 20, 2012 flu vaccination. Id.

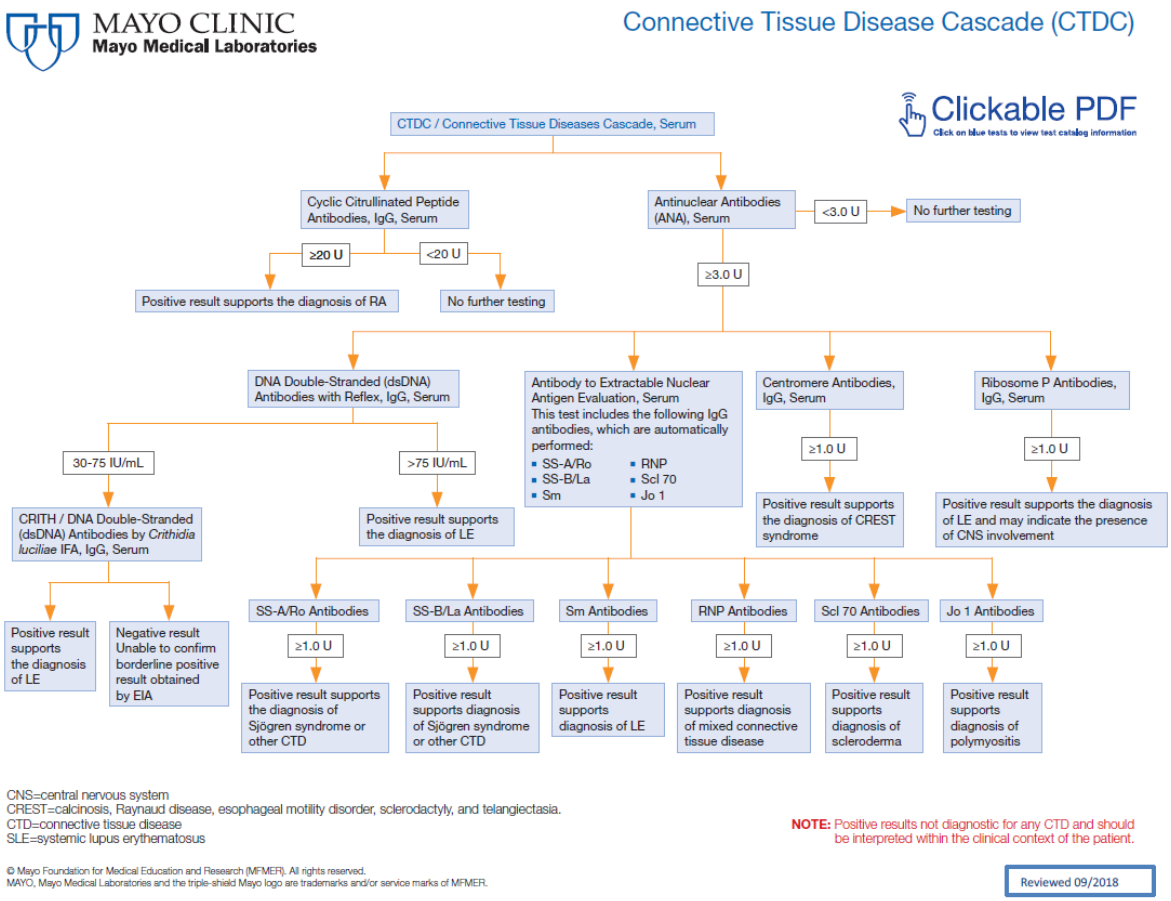
Dr. Matloubian points out that people who receive the anti-TNF medications which petitioner took in early 2013 have themselves suffered MCTD as a consequence of the medication, citing Ex. A, Tab 4, at 1. Thus medical literature associates the medication petitioner received in 2013 with development of symptoms diagnosed as MCTD. Id.

Dr. Matloubian comments that when petitioner requested Dr. Tsai, her allergist, to write a

statement that flu vaccine caused her MCTD, Dr. Tsai did an independent search of the medical literature and concluded there was no association between flu vaccine and MCTD. Dr. Tsai refused to amend his records to state petitioner's flu vaccine caused her MCTD. Id. at 6.

Articles filed after the hearing

Petitioner filed as Exhibit 105, to which Dr. Ahmed referred in his written rebuttal (Ex. 103, at 2), a one-page PDF from the Mayo Clinic, entitled Connective Tissue Disease Cascade (CTDC), attached to Test ID: CTDC Connective Tissue Diseases Cascade, Serum. Clinical and Interpretive in MAYO CLINIC MAYO MEDICAL LABORATORIES, http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83631 (last visited September 10, 2018).



Id. The chart is arranged in order of importance. The top listing of tests can determine if a patient has RA (which is irrelevant in the instant case) or MCTD. But the Mayo Clinic says

that if someone's ANA tests less than 3.0 U (<3.0 U)[107] he or she does not need further testing because he or she does not have MCTD. If, however the test of ANA were more or equal to 3.0 U (≥3.0 U), then further testing would be necessary to diagnose MCTD.

The next level of testing includes an evaluation of antibody to extractable nuclear antigen (ENA), including the following IgG antibodies, which are automatically performed: SS-A/Ro, SS-B/La, Sm, RNP, SCL 70, and Jo 1. The testing also includes DNA double-stranded (dsDNA) antibodies with reflex, IgG, serum; centromere antibodies, IgG, serum; and ribosome P antibodies, IgG, serum.

Petitioner's Nuclear AB Panel testing on October 3, 2012 (Ex. 3, at 41) was negative for dsDNA antibody; Sjögrens-A and –B antibody; Smith IgG; chromatin (nucleosomal) antibody; ribosomal P antibody; centromere antibody; Sm antibody+RNP antibody; Scl-70 antibody; and Jo-1 antibody. Id. Her RNP antibody was positive at 1.2 (when the normal result is less than 1.0). Id.

The contrary result in petitioner's serum testing negative for IgG antibodies yet weakly positive for RNP antibody prompted Dr. Matloubian to call the weakly positive RNP antibody a false positive because petitioner's test results were internally inconsistent.

DISCUSSION

To satisfy her burden of proving causation in fact, petitioner must prove by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of Health and Human Services, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause of and effect showing that the vaccination was the reason for the injury [,]" the logical sequence being supported by a "reputable medical or scientific explanation[,]" i.e., "evidence in the form of scientific studies or expert medical testimony[.]"

418 F.3d at 1278.

Without more, "evidence showing an absence of other causes does not meet petitioner's affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal

[107] The Mayo Clinic does not use ratios in its determination of reference values for the CTDC algorithm. It specifies in its description for CTDC reference values that < or =1.0 U is negative; 1.1-2.9 U is weakly positive; 3.0-5.9 U is positive; and > or =6.0 U is strongly positive. TEST ID: ANA2 ANTINUCLEAR ANTIBODIES (ANA), SERUM, Reference Values, https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9026 (last visited October 12, 2018).

association is not sufficient to prove causation in fact. Id. at 1148.

Petitioner must show not only that but for flu vaccine, she would not have MCTD, but also that flu vaccine was a substantial factor in causing her MCTD. Shyface v. Sec'y of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

An analysis of the multiple issues in this case is going to seem like the quantum physics thought experiment of Schrödinger's cat[108] in which a cat was both alive and dead at the same time. In other words, various facts, test results, and analyses in this case seem at the same time to indicate nothing and something.

Considering the Opinions of Treating Physicians

The Federal Circuit in Capizzano, 440 F.3d at 1326, emphasized that the special masters are to evaluate seriously the opinions of petitioner's treating doctors since "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." See also Broekelschen v. Sec'y of HHS, 618 F.3d 1339, 1347 (Fed. Cir. 2010); Andreu v. Sec'y of HHS, 569 F.3d 1367, 1375 (Fed. Cir. 2009). Petitioner's treating rheumatologist Dr. Lin diagnosed petitioner with mixed connective tissue disease. The consulting rheumatologist Dr. Lau diagnosed petitioner with undifferentiated connective tissue disease. Another consulting rheumatologist Dr. Patel diagnosed petitioner with connective tissue disease. Three different rheumatologists at three different times diagnosed petitioner with some type of connective tissue disease. Their diagnoses are strong evidence that petitioner has connective tissue disease, either mixed, undifferentiated, or just connective. As for vaccine causation, Dr. Tsai, petitioner's treating allergist/immunologist, advised her never to have another flu vaccination, but when petitioner asked him to write in his notes that flu vaccine caused her connective tissue disease, after a review of the medical literature, he refused to do so. Dr. Lin repeatedly wrote in her records that petitioner was allergic to flu vaccine both in 1999 and 2012. However, these notes were a consequence of petitioner's history to Dr. Lin, not Dr. Lin's objective opinion. Moreover, since petitioner's left arm pain in 1999 was due to supraspinatus tendinitis, she had SIRVA, which is a mechanical injury due to the vaccination being given too high rather than a reaction to the components of the vaccine. SIRVA has nothing to do with a rheumatic reaction to vaccine, not to mention that petitioner had no reaction whatsoever to her 2009 flu vaccination. The concept that petitioner gave to her treating doctors Lin and Tsai so that they wrote down she was allergic

[108] Erwin Schrödinger received the Nobel Prize in physics in 1933 and is best known for his work regarding quantum theory. He created the thought experiment of a cat in a steel box with other items to illustrate the nature of wave particles. Schrödinger posited a cat, poison, a Geiger counter, radioactive material, and a hammer inside of the steel box. The amount of radioactive material was so small, there was only a 50-50 chance of its being detected over the course of an hour. However, if the Geiger counter detected radiation, the hammer would smash the poison, killing the cat. Until someone opened the box and observed what was inside, no one knew if the cat were alive or dead. Thus, until the system collapsed into one configuration, the cat seemingly would be both alive and dead. The Physics Behind Schrödinger's Cat Paradox, NATIONAL GEOGRAPHIC, https://news.nationalgeographic.com/news/2013/08/130812-physics-schrodinger-erwin-google-doodle-cat-paradox-science/ (last visited November 2, 2018).

to flu vaccine is invalid as to the 1999 and 2009 flu vaccinations. The only issue is whether or not she had an adverse reaction to the components of her 2012 flu vaccine.

The Federal Circuit stated that Congress, in passing the National Childhood Vaccine Injury Act, envisioned a system "in which close calls regarding causation are resolved in favor of injured claimants." Althen, 418 F.3d at 1280. The analysis of the case includes resolving the question of whether this case involves a close call.

The case involves three issues:

1. Did petitioner ever have MCTD?
2. If she did not have MCTD, what if anything, did she have and when did it begin?
3. What caused whatever petitioner has?

Did Petitioner ever have MCTD?

On March 3, 2008, petitioner went to her PCP at the time, Dr. Mary Regan at Samaritan Family Practice, complaining of one month of aching in her fingers and thumbs bilaterally, and head and chest congestion for three days. Dr. Regan pondered whether petitioner's fingers were slightly swollen, noting that petitioner had a family history of rheumatoid arthritis in her grandmother. Petitioner's physical examination was unremarkable except for mild nasal congestion. Dr. Regan referred petitioner to testing to see if she had a positive ANA and a positive rheumatoid factor. Petitioner had a positive ANA of 1:160 in 2008, but her rheumatoid factor was negative and her erythrocyte sedimentation rate was normal. Dr. Regan referred petitioner to a rheumatologist, Dr. Carter V. Multz, whose records petitioner did not file. He died on August 7, 2013.

On January 20, 2011, petitioner saw TK at Samaritan Family Practice, complaining of one to two months of fatigue. She had right shoulder pain and trouble lifting her arm for two to three months.

On March 17, 2011, petitioner saw a doctor at Samaritan Family Practice, complaining of foot and shoulder pain. On June 15, 2011, petitioner told TK at Samaritan Family Practice that her right shoulder had been painful for nine months.

On January 26, 2012, petitioner saw Dr. Jing Qing Xu of Kaiser Permanente as a new patient. Petitioner had chronic pain syndrome and shoulder joint pain. She had chronic left shoulder pain.

On March 16, 2012, petitioner called Dr. Xu, stating that she had been feeling acid reflux and Dr. Xu diagnosed petitioner with gastroesophageal reflux.

On August 13, 2012, petitioner saw Dr. Xu, telling Dr. Xu she had pain in her left arm and right shoulder intermittently for a long time. Dr. Xu diagnosed petitioner with impingement

syndrome of the shoulder.

On September 20, 2012, petitioner received the flu vaccine at issue.

In October 3, 2012, petitioner saw Dr. Xu, complaining of still having pain in her joints, knees, hands, and lower back, but her shoulder pain was improving. Dr. Xu diagnosed petitioner with chronic sinusitis and osteoarthritis of the hand. She sent her for antibody testing, all of which proved negative except for the ANA which was one dilution greater than it had been in 2008, at 1:320, and a slightly positive anti-RNP antibody test at 1.2. Dr. Xu did not realize that the anti-RNP antibody test result was an anomaly because petitioner should have had a positive dsDNA antibody if she were positive for anti-RNP antibodies. But then Dr. Xu is not a rheumatologist.

Dr. Xu sent petitioner to Dr. Lin, a rheumatologist, also at Kaiser Permanente, whom petitioner saw on October 31, 2012, five weeks after petitioner's flu vaccination. Petitioner complained of joint pain in her hands, knees, and toes with prolonged morning stiffness for many months. She had a history of redness of her face, nasal bridge, and chin, as well as dry eyes and mouth, and extreme fatigue. On physical examination, petitioner had bilateral proximal-interphalangeal and metacarpal-phalangeal joint tenderness, ulnar deviation, and bilateral knee tenderness.

Dr. Lin diagnosed petitioner with MCTD even though the testing for anti-RNP antibodies was an anomaly in light of the negative dsDNA testing, and even though the 1.2 test result was just above the normal limit and medical literature requires a high titer in order to diagnose a patient with MCTD, and also requires a high titer ANA, which petitioner did not have. Because Dr. Lin diagnosed petitioner with MCTD which can lead to lung disease, Dr. Lin had petitioner undergo chest x-rays to look for interstitial lung disease, and the result was normal. Dr. Lin ignored petitioner's negative C-reactive protein rest result, and negative erythrocyte sedimentation rate, both indicators of inflammation had they been positive. Dr. Lin ignored all the other negative antibody results in the test results to justify a diagnosis of rheumatic disease. Instead of retesting petitioner and using a better test than the BioPlex bead test, i.e., ELISA, Dr. Lin put petitioner on Plaquenil, an anti-inflammatory used for lupus and RA, and prednisone, a steroid. According to petitioner's testimony, Dr. Lin told her she had little in petitioner's testing to justify her diagnosis and Dr. Lin really was not sure what petitioner had, but Dr. Lin felt she had to treat petitioner's symptoms aggressively as soon as possible to avoid petitioner's getting worse.

The undersigned is impressed with the testimony of both petitioner's expert Dr. Ahmed and respondent's expert Dr. Matloubian who agreed that, had they seen petitioner on October 31, 2012, they would not have diagnosed her with MCTD. Dr. Ahmed said he would have diagnosed petitioner with early undifferentiated connective tissue disease if not early overlap syndrome. Tr. at 198. Dr. Matloubian said he would not have diagnosed petitioner with any rheumatic disease at all. He said petitioner had the same symptoms pre-vaccination as post-vaccination: fatigue, musculoskeletal pain in many joints, including her hands, and tightness and

numbness in her hands. Id. at 245-46. Dr. Matloubian said he does not know what petitioner has. Id. at 274.

Moreover, both Dr. Ahmed and Dr. Matloubian testified that had they seen petitioner on October 31, 2012, they would not have prescribed medication. Dr. Ahmed said he would have retested her to see if she had anti-RNP antibody before giving her high-dose steroids or Methotrexate. Id. at 198. Dr. Matloubian said if he had seen petitioner, he would also have retested her but with the ELISA assay, which is more sensitive and more specific for detecting anti-RNP antibodies that the multiplex bead assay petitioner underwent. Id. at 263.

Dr. Ahmed said that someone taking an immunosuppressant such as Enbrel runs the risk of having autoimmune symptoms from the drug. Id. at 199. Dr. Matloubian agreed in a supplemental expert report filed after the hearing. Ex. F, at 5. The medical records reflect that petitioner had Raynaud's phenomenon not when Dr. Lin diagnosed her with MCTD on October 31, 2012, but two years later. It would indeed be a paradox if, instead of helping petitioner improve, her drug therapy made her condition worse. Her three rheumatologists, Dr. Lin, Dr. Lau, and Dr. Patel, came to three different conclusions as to what rheumatologic disease she has: MCTD (Lin), overlap syndrome or undifferentiated CTD (Lau), or CTD (Patel). As Dr. Matloubian pointed out, petitioner's physical examination findings differed depending on which rheumatologist performed the exam. He had recommended petitioner go to a rheumatologist at a tertiary care center such as Stanford or UCSF, where petitioner's medical care would be superior to what she was receiving, but petitioner did not go.

Although the undersigned emphasizes above the points upon which Dr. Ahmed and Dr. Matloubian agreed, they disagreed vehemently in the rest of the case, including in the 10 expert reports filed before and after the hearing. Petitioner filed Exhibits 67, 70, and 87 before the hearing, and Exhibits 103 and 110 after the hearing, all by Dr. Ahmed. Respondent filed Exhibits A, C, and D before the hearing, and Exhibits F and G after the hearing, all by Dr. Matloubian.

Because Dr. Ahmed's clinical practice as a rheumatologist ended in June 2008, more than 10 years ago, and Dr. Matloubian is still actively engaged as a rheumatologist, the undersigned finds Dr. Matloubian's opinion about whether petitioner has MCTD more persuasive. The overwhelming majority of the medical articles supports the conclusion that petitioner does not have MCTD.

Moreover, Dr. Ahmed's opinion was frequently inconsistent. He would assert one point in an expert report and then say the opposite point at the hearing. For instance, in his first report, he asserted that petitioner's first flu vaccination (first, that is, in the medical records) on October 7, 1999 primed her immune system, her second flu vaccination on October 14, 2009 further boosted her asymptomatic autoimmunity, and then her third flu vaccination on September 20, 2012 transformed her underlying autoimmunity into an autoimmune disease, i.e., MCTD. Ex. 67, at 7. At the hearing, he said he would not necessarily call petitioner's flu vaccination in 1999 and flu vaccination in 2009, 10 years later, a prime/boost. Tr. at 64.

In addition, Dr. Ahmed placed great emphasis on petitioner's positive ANA of 1:160 in 2008 while at the same time agreeing with Dr. Matloubian that a positive ANA can have no clinical value because people without autoimmune disease also can have it. This devolved into a dispute over whether the homogeneous pattern was significant or not as to whether the ANA denoted an autoimmune illness such as MCTD or denoted petitioner's hypothyroidism, which Dr. Matloubian termed Hashimoto's thyroiditis. While the ANA of 1:320 in 2012 was only one dilution greater, both the 2008 and 2012 ANA had a homogeneous pattern, which Dr. Matloubian attributed to petitioner's hypothyroidism but which Dr. Ahmed posited could just mean that the homogeneous pattern hid a speckled pattern. Then he denied a patient's ANA had to have a speckled pattern in order to merit a diagnosis of MCTD. But then he said that petitioner did not have MCTD until after her 2012 flu vaccination. Dr. Ahmed seemed always to be looking for exceptions to what the medical literature, including criteria for diagnosing MCTD, require.

He denied that there was an anomaly in the 2012 antibody testing when the anti-RNP antibodies result was contradictory to the smDNA result, yet the same bead in the BioPlex assay tested both. Either both antibodies should have been positive or both negative. He denied that the lack of inflammatory markers in the ESR, CRP, and other autoantibodies tested in 2012 was of any significance. He never even broached the matter that petitioner failed to have another marker for MCTD listed in the medical records: hyperglobulinemia. While he was denying the significance of all the serologic testing that showed petitioner was normal, he insisted that she had nothing pre-vaccination in 2012 to indicate that the onset of her supposed MCTD was before the flu vaccination on September 20, 2012.

There are Schrödinger's cats all through Dr. Ahmed's line of reasoning. The 2008 ANA of 1:160 means something. It means nothing. The homogeneous pattern of her ANA means something. It means nothing.[109] Her lack of any valid inflammatory marker except a positive ANA means something. It means nothing. Her weakly positive anti-RNP antibodies measured only once in 2012 means something. It means nothing. The prior flu vaccinations in 1999 and 2009 mean something in terms of priming and boosting. They mean nothing. The presence of anti-RNP antibodies is the sine qua non of diagnosing MCTD. The lack of anti-RNP antibodies because petitioner's 2012 test is a false positive means nothing because petitioner can have MCTD without them.[110] This constant switching back and forth in Dr. Ahmed's opinion

[109] Dr. Ahmed was consistent in his view that the homogeneous pattern of petitioner's positive ANA of 1:160 in 2008 masked an underlying speckled pattern, as if to prove that petitioner had anti-RNP antibodies in 2008. But according to Arbuckle (Ex. 28), the presence of anti-RNP antibodies appears in the sera of those tested one year and one-half before clinical manifestations, unlike the much longer appearance of positive ANA before clinical signs appear. If this is so and petitioner's homogeneous pattern in 2008 masked a speckled pattern of anti-RNP antibodies petitioner's onset of clinical symptoms of MCTD should have appeared in 2009, which would prove the onset of her alleged MCTD was before her 2012 flu vaccination, a position Dr. Ahmed does not take.

[110] As the undersigned explains in supra n.105, Dr. Ahmed's sur-rebuttal statement, Ex. 110, at 113, remarks that there is an article among the 25 references Dr. Matloubian made in his initial expert report (Ex. A), but Dr. Ahmed identifies this article only as Ex. A, Table 4, at 118 without indicating what the reference number is. His point is that 15 out of 16 patients had positivity to both Smith+RNP and RNP which means one person did not. Therefore

expressed in his expert reports and testimony underscores either a lack of preparation, a lack of experience (this being his first time testifying in court), or a lack of support for his opinion in the medical records and/or medical literature. It seems to the undersigned that Dr. Ahmed takes the view that whatever the medical records and literature say, petitioner prevails because nothing really is significant since the opposite can be true. This is not how one builds credibility.

Dr. Ahmed made fundamental errors. At the hearing, he said petitioner manifested an elevated CRP and elevated C3 and C4 complement levels at the time she presented to Dr. Xu and Dr. Lin post-2012 flu vaccination. But those markers of inflammation were abnormal only on May 14, 2013, seven and one-half months after Dr. Xu had petitioner undertake serological testing. That was the only time they were abnormal and Dr. Matloubian posited a simple cold could have caused those results. Dr. Ahmed also said petitioner manifested Raynaud's in October 2012, but she did not manifest Raynaud's until November 2014, two years after her post-2012 flu vaccination visits to Dr. Xu and Dr. Lin. Moreover, in his reports, he confused the clinical signs of Raynaud's phenomenon as manifesting in the palms and bottoms of the feet which is incorrect. Raynaud's manifests in the fingers and toes. The undersigned recognizes that Dr. Ahmed left clinical rheumatology practice 10 years ago and may be unfamiliar with Raynaud's, but taking on the role of expert means being an expert. Theories are not sufficient without factually accurate support. Numerous medical articles emphasize that the appearance of Raynaud's occurs early in clinical manifestations of MCTD, but petitioner's Raynaud's did not occur until two years after her alleged first manifestations to Dr. Xu and Dr. Lin.

The undersigned finds particularly concerning his focusing on Dr. Lin's second "correction" to her medical record of October 31, 2012 at petitioner's insistence when she visited Dr. Lin on January 5, 2016 so that Dr. Lin wrote petitioner's onset of symptoms of MCTD occurred after her September 20, 2012 flu vaccination and not before (as she had originally written on October 31, 2012 when she noted onset many months earlier, only to change that to two months earlier, i.e., in August 2012, neither of which onset was acceptable to petitioner).

In Exhibit 110, Dr. Ahmed takes this obvious attempt of petitioner to skew the medical records in her favor so as to put symptoms post-vaccination instead of pre-vaccination as indicative of a true reflection of Dr. Lin's mind rather than petitioner's persistence in getting Dr. Lin to change her record. Ex. 110, at 3. This "finally" true reflection of Dr. Lin's mind came over three years and two months after Dr. Lin wrote her original notes. The only impression the undersigned can have to this warping of the truth is that Dr. Ahmed was committed to finding onset after the 2012 flu vaccination and he was at pains to find a reason to do so, grasping at the straw Dr. Lin provided when she relented (after previously failing to relent when she initially "corrected" the onset to two months or August 2012).

Dr. Ahmed throws in another Schrödinger cat for good measure. In case the undersigned rules that petitioner's onset of MCTD occurred pre-2012 flu vaccination (although he does not believe it did), the 2012 flu vaccination caused petitioner significant aggravation. Thus the

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he concludes petitioner's failure to have a positive antibody to both Smith+RNP and RNP does not matter. The undersigned cannot find that article after looking at all 25 references. The only proof is that it does matter.

symptoms and ANA test result pre-2012 flu vaccination medical records mean nothing. The symptoms and ANA test result pre-2012 flu vaccination records mean something.

What if anything did Petitioner have and when did it begin?

It is important to remember that Arbuckle (Ex. 28) determined through an analysis of servicemen's sera predating any diagnosis of clinical SLE that they had a positive ANA at least nine years earlier. Testimony in this case reveals that use of steroids can mask symptoms. Thus it is intriguing to note that after petitioner injured her back on December 15, 2000, Dr. Joel S. Saal, an orthopedist, injected petitioner with Decadron, a glucocorticoid, on April 24, 2002 because she was still complaining of pain. On July 11, 2002, Dr. Saal again injected petitioner with Decadron and injected her as well with another glucocorticoid, Depo-Medrol.

Dr. Matloubian testified that if someone is a smoker, her risk of RA increases by 60 fold. Id. at 254. Petitioner was a smoker. Both experts recognized that petitioner's family history is replete with individuals with autoimmune disease: her grandmother has rheumatoid arthritis, her mother has Hashimoto's thyroiditis (which Dr. Matloubian thinks petitioner has as well), and her sister has Sjögren's. If anyone would be prone to developing an autoimmune disease, it would be petitioner.

From the evidence before the undersigned in the medical records, medical literature, and in the expert reports and expert testimony, the undersigned finds that petitioner has, as Dr. Ahmed posited in his testimony, and Dr. Lau (her second rheumatologist) considered in his differential diagnosis, UCTD which is so mild as not to warrant treatment, but which over time has progressively become more noticeable as it has worsened, possibly due to the effects of some of petitioner's quite serious medications. Petitioner's only filed antibody and serological testing done in October 2012 was completely devoid of inflammatory markers or antibodies, except that her ANA was 1:320, and she had a false positive anti-RNP antibody titer of 1.2. It is conceivable that she might never have warranted treatment.

As for the onset, the undersigned suspects petitioner's UCTD began symptomatically in December 2005 when Dr. Saal, an orthopedist, noted that petitioner had undergone a number of laboratory tests so that Dr. Fred Orcutt, an orthopedic surgeon, could exclude the possibility that she had rheumatic disease or multiple myeloma. Petitioner never filed Dr. Orcutt's medical records or the laboratory test results Dr. Orcutt had her undergo. He retired and his medical group said no records predating 2010 were available. Ex. 120. Petitioner has kept the results of these medical tests to herself. It is intriguing, however, that Dr. Orcutt entertained the possibility that petitioner had rheumatic disease as early as 2005, seven years before her 2012 flu vaccination.

Three years later after Dr. Orcutt entertained the possibility that petitioner had rheumatic disease, petitioner complained on March 3, 2008 to Dr. Mary Regan at Samaritan Family Practice of having one month of aching in her fingers and thumbs bilaterally. Dr. Regan saw what looked like slightly swollen fingers. She referred petitioner to Dr. Carter V. Multz, a

rheumatologist, but petitioner did not file his records on March 13, 2015 when she filed a petition and he died August 7, 2013. Whether she could have ever filed his records is unknown. The results of the March 5, 2008 lab tests were a normal ESR, negative rheumatoid factor, and positive ANA of 1:160 with a homogeneous pattern. Petitioner would know what Dr. Multz told her but she has not revealed anything. Presumably, the Samaritan Family Practice medical records would have recorded a rheumatologic diagnosis if someone had made it.

These sparse records reveal that different medical treaters entertained the possibility of petitioner's having a rheumatologic illness because of some type of symptom (Dr. Orcutt) or slightly swollen fingers (Dr. Regan). According to the Arbuckle article (Ex. 28), it can take many years for someone with a positive ANA to have clinical symptoms. These records signify to the undersigned that petitioner was gradually manifesting symptoms of a UCTD and she continued to have benign lab test results and intermittent problems with her fingers as her UCTD became more apparent.

Althen Analysis

Prong One

Dr. Ahmed has three bases for saying flu vaccine caused petitioner's MCTD. His first basis for saying flu vaccine caused petitioner's MCTD was she was much older than younger women who manifest MCTD. However, since the undersigned rejects that petitioner has MCTD, her age of onset is no longer a factor. Moreover, since Arbuckle (Ex. 28) posits the appearance in sera years before clinical symptoms of rheumatologic disease, the clinical symptoms do not mark the beginning of the onset of rheumatologic disease.

Dr. Ahmed's second basis for saying flu vaccine caused petitioner's MCTD is molecular mimicry. But, as Dr. Matloubian said, Dr. Ahmed's explanation for molecular mimicry is too simplistic, relying on a two-dimensional understanding instead of recognizing that proteins fold within themselves and are therefore not available for mimicry by an antigen with the same proteins. Dr. Matloubian said Dr. Ahmed's diagram in Exhibit 25 is too simplistic and does not convey that a similar linear sequence of amino acids in one protein may be hidden within its three-dimensional structure and not accessible to antibodies. Thus sequence homology is insufficient evidence for molecular mimicry. Ex. A, at 12.

It is curious that Dr. Ahmed, writing for a professional journal, and not testifying for petitioner disagrees with himself as an expert witness on the risk of molecular mimicry to vaccinees. In his article Assessing the Safety of Adjuvanted Vaccines, he and his co-authors write vaccine antigens are screened for molecular mimicry to exclude autoantigens in vaccines intended for humans. Ex. 57, at 2. Dr. Ahmed and his co-authors also state that there exists the risk for coincidental association with naturally occurring autoimmune disease after vaccination. Id. at 5. That coincidence is exactly what the undersigned finds to have happened in this case most especially because of the flawed third basis for Dr. Ahmed's opinion on causation.

Dr. Ahmed's third basis is the Guldner article (Ex. 79), positing that flu B strain virus stimulates autoimmune reaction. Dr. Matloubian did a search of how many times others have cited this article since its publication in 1990. The result was 10 times, a comment on its poor academic worth or as Dr. Matloubian put it an indicator that it is not valid or have biologic importance. Ex. C, at 10; see also Ex. F, at 7. Dr. Matloubian also notes that the Guldner article has methodologic flaws leading to antibody cross-reactivity having no biological significance. Ex. F, at 7.

In his testimony, Dr. Ahmed said that the major antigen identified with MCTD is either the 68 or 70 kilodalton protein which is called U1-RNP. Tr. at 222. The Guldner article[111] focuses solely on anti-p68 autoantibodies and not on anti-p70 autoantibodies. The undersigned has not seen any testing of petitioner to detect whether she has either anti-p68 autoantibodies or anti-p70 autoantibodies. Moreover, the Guldner article deals with flu B virus, not killed virus vaccine. As Dr. Ahmed testified, killed virus flu vaccines are not contraindicated for persons with rheumatic disease. Tr. at 215.

The undersigned finds it unlikely that the Guldner article is relevant to the issue of causation. Dr. Matloubian states in Exhibit C, at 9:

> The primary goal of this study, which was published in 1990, was to define the multiple sequences in the U1 RNP that are recognized by antibodies. They found that a fraction of the sera of patients with MCTD or lupus (8 out of 37) recognized a sequence of 5 amino acids in U1 RNP. Using a computer search they found a similar 5 amino acid sequence in the matrix protein of influenza B virus. Then they boiled the influenza proteins and ran them on a gel and showed that serum from one patient can recognize the influenza protein, albeit very weakly (Ex. 79 at 6 [internal page 824]). This assay i[s] not very physiologic since boiling of proteins changes their structure and exposes sequences that were previously hidden from antibodies. … The authors never asked whether this same sequence is on the surface of the matrix protein or buried inside and inaccessible.

Dr. Ahmed testified no one knows if anti-RNP antibodies cause disease, i.e., that they are pathogenic. Tr. at 214-15. Dr. Matloubian stated that the presence of anti-RNP antibodies is not pathogenic, i.e., their presence does not cause the disease but is merely a marker of the disease. Tr. at 288, 320. Therefore, Dr. Ahmed's basing a theory of causation on the Guldner article makes no sense since the appearance of a marker of disease such as anti-RNP antibodies does not indicate the marker caused the disease. The fact that someone whose sera containing anti-p68 antibodies may respond to the flu B virus M1 matrix is irrelevant to the issue of causation if that marker does not cause or worsen the person's rheumatic disease.

[111] The title of the article is Human Anti-P68 Autoantibodies Recognize a Common Epitope of U1 RNA Containing Small Nuclear Ribonucleoprotein and Influenza B Virus.

Moreover, Guldner's article partially involves experimentation on mice. Dr. Ahmed said that applying to a human what a scientist learns with animal models does not work because the distribution of immune receptors in animals is not the same as in humans and the genetics in animals is not the same as in humans. Tr. at 44-45. As for the people whose sera responded to the flu B strain virus Guldner tested, he divided a group of sera from which only a subset (8 out of 37) had anti-p68 autoantibodies that recognized an epitope shared by flu B virus M1 matrix protein. Ex. 79, at 824. However in the sera of healthy individuals and the anti-p68 sera of individuals with various rheumatic diseases and high titers of autoantibodies to other antigens (e.g., Sm, Ro, La, centromere, topoisomerase I, PM-Scl, histones, dsDNA, fibrillarin, Jo-1), Guldner did not find the requisite antibodies to the flu B virus M1 matrix protein. Id. Guldner does not comment on the surprising lack of autoantibody response of the anti-p68 sera of individuals with various rheumatic diseases and high titers of autoantibodies to other antigens. One would think that they of all people would be the most sensitive in responding to the flu B virus M1 matrix protein.

Guldner's broad conclusions from minimal data are speculative, as Guldner admits. Id. at 826. Guldner finds consistent with his speculation that two anti-p68 autoimmune patients had high titers of antibodies in early sera that dropped to undetectable levels during progression of their rheumatic disease. Id. Guldner suggests further investigation of his hypothesis of autoimmune response by molecular mimicry in persons infected or vaccinated with flu B viruses. Id.

If indeed Dr. Ahmed believes (since he has both proposed it and denied it) that petitioner's prior flu vaccinations in 1999 and 2009 primed and boosted her immune response to her 2012 flu vaccination, resulting in MCTD, the undersigned finds that basis not credible. Petitioner had supraspinatus tendinitis (conceivably SIRVA), which is not a rheumatologic disease, one day after receiving her 1999 flu vaccination, manifesting as pain in her left arm and the inability to raise it. Petitioner did not have any adverse reaction to her 2009 flu vaccination. Her 2009 flu vaccination was just one year after she was noted to have a positive ANA of 1:160, when it might be reasonable to expect an autoimmune reaction since she had one marker of autoimmunity (or it does not mark autoimmunity as both experts agreed). There is no credible reason to associate these three vaccinations over 13 years with a priming or boosting effect.

The undersigned finds that petitioner has failed to provide a credible medical or scientific theory explaining a causal connection between flu vaccine and either MCTD or UCTD.

Prong Two

Since petitioner has failed to provide a credible medical or scientific theory explaining a causal connection between flu vaccine and either MCTD or UCTD, petitioner has also failed to prove a logical sequence of cause and effect showing that her 2012 flu vaccination caused her MCTD or UCTD.

Prong Three

Temporal association is not sufficient to prove causation. Since the undersigned finds that petitioner manifested clinically UCTD before her 2012 flu vaccination, this discussion should be about significant aggravation. But if the undersigned were to hold that the onset of her UCTD began two weeks or a few weeks post-vaccination, it is hard to say that is an appropriate temporal interval without also saying that flu vaccine can cause UCTD (Prong One of Althen).

Does Petitioner Satisfy the Loving Criteria?

The Federal Circuit in W.C. v. Sec'y of HHS, 704 F.3d 1352, 1357 (Fed. Cir. 2012), adopted the test in Loving v. Sec'y of HHS, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009), as "the correct framework for evaluating off-table significant aggravation claims." The Vaccine Act, 42 U.S.C. § 300aa-33(4), defines "significant aggravation" as follows: "The term 'significant aggravation' means any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health."

The Loving test has six parts:

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

Parts three to six are the correlate of Althen prongs one to three which the undersigned finds petitioner did not succeed in proving. That leaves parts one to three of the Loving criteria to analyze:

(1) Before her 2012 flu vaccination, petitioner complained of pain, fatigue, numbness in her fingers, aching in her fingers and thumbs bilaterally, and gastroesophageal reflux disease, and was noted to have slightly swollen fingers and an ANA of 1:160. After her 2012 flu vaccination, petitioner complained of pain (but improvement of her shoulder pain), fatigue, prolonged morning stiffness for many months, and was noted to have finger tenderness and an ANA of 1:320. The undersigned does not see a markedly greater disability, pain or illness accompanied by substantial deterioration of health in comparing petitioner's pre-2012 flu vaccination history to her post-flu vaccine histories she gave to Dr. Xu on October 3, 2012 and to Dr. Lin on

October 21, 2012. On starting medication, petitioner's condition began to worsen with the addition of Raynaud's phenomenon two years later;

(2) petitioner's current condition is in maintenance mode purportedly due to regular Actemra IV infusions;

(3) it is hard to determine if petitioner's current condition is a substantial deterioration of her health. If she went off Actemra, as Dr. Patel (petitioner's third rheumatologist) suggested, she might be more accurately diagnosed and treated, but petitioner refuses to do that because Dr. Lin said if she went off Actemra, she could not then go back on.

The undersigned finds that petitioner has failed to satisfy the Loving criteria for proving significant aggravation. This case is not a close call under either an Althen analysis or a W.C. analysis using the Loving criteria.

The undersigned's opinion in no way detracts from petitioner's sincere belief that the 2012 flu vaccination changed her life for the worse. However, the medical records, majority of the medical literature, and more persuasive opinion of Dr. Matloubian over that of Dr. Ahmed lead the undersigned to find no credible support for petitioner's own view of causation.

The undersigned **DISMISSES** this case for failure to make a prima facie case of causation or, in the alternative, of significant aggravation.

CONCLUSION

This petition is **DISMISSED**. In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of Court is directed to enter judgment herewith.[112]

IT IS SO ORDERED.

Dated: December 20, 2018

/s/ Laura D. Millman
Laura D. Millman
Special Master

[112] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party, either separately or jointly, filing a notice renouncing the right to seek review.