In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-1213V
Filed: July 11, 2023
PUBLISHED

JODILYN DRUERY,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Andrew Donald Downing, Downing, Allison & Jorgenson, Phoenix, AZ, for petitioner.
Andrew Henning, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On September 7, 2017, petitioner, Jodilyn Druery, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that an influenza ("flu") vaccine she received on October 26, 2016, caused her to suffer an acute cardiovascular event, likely myocardial infarction, resulting in ventricular fibrillation and implantation of a defibrillator. For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make several factual demonstrations, including showing that an individual received a vaccination covered by the statute;

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

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

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

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

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

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

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be based upon "sound and reliable" medical or scientific explanation. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The *Althen* court also indicated that, in finding causation, a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280.

II. Procedural History

As noted above, petitioner filed her petition on September 7, 2017. Within the petition, she acknowledged that her medical records are unclear with respect to a specific diagnosis for her acute cardiovascular event. (ECF No. 1, p. 4.) The petition was accompanied by an affidavit marked as Exhibit 1. Petitioner filed medical records marked as Exhibit 2-14 and then filed a Statement of Completion on October 24, 2017. (ECF No. 10.) The case was initially assigned to Special Master Roth and then to Special Master Oler. (ECF Nos. 4, 15.)

Between January and April of 2018, petitioner filed additional medical records marked as Exhibits 15-19. Thereafter, respondent filed his Rule 4 Report. (ECF No. 20.) Respondent recommended against compensation, raising, *inter alia*, the issue of diagnosis and also including several requests for additional records. (*Id*.) Petitioner filed further medical records marked as Exhibits 20-24 in June and July of 2018. (ECF Nos. 21-22, 24.) In August of 2018, petitioner filed an expert medical opinion by cardiologist Robert Stark, M.D. (ECF No. 25; Exs. 25-26.) Dr. Stark opined that petitioner suffered an acute myocardial infarction caused by vaccine-related coronary endothelial dysfunction. Petitioner filed further medical records marked as Exhibit 27 in January of 2019. (ECF No. 28.)

Between December of 2018 and March of 2019, respondent filed responsive expert reports and supporting literature by cardiologist Shane LaRue, M.D., and immunologist Noel Rose, M.D., Ph.D. (ECF Nos. 27, 29-32; Ex. A-D.) Dr. LaRue agreed that petitioner likely suffered a myocardial infarction, but further specified that it

constituted "MINOCA" or "myocardial infarction with no obstructive coronary atherosclerosis." (Ex. A, p. 5.) Both of respondent's experts disagreed that the flu vaccine played any role. In August of 2019, petitioner filed a supplemental report by Dr. Stark responding to respondent's experts as well as an additional report by immunologist David Axelrod, M.D., and supporting literature. (ECF Nos. 36-40; Exs. 28-56.)

Thereafter, Special Master Oler issued an order directing Drs. Stark, LaRue, and Rose, to answer specific questions. (ECF No. 41.) Respondent filed a supplemental report by Dr. LaRue in December of 2019 and a supplemental report by Dr. Rose in January of 2020. (ECF No. 42; Ex. E and ECF No. 57; Ex. F.) Petitioner filed a supplemental report by Dr. Stark in January of 2020. (ECF No. 45; Ex. 58.) An entitlement hearing was then set for June of 2021 and petitioner filed further medical records marked as Exhibits 59-61 in the interim. (ECF No. 51.) However, on September 8, 2020, respondent advised that Dr. Rose had passed away. (ECF No. 57.) Respondent filed a report by a different immunologist, Arnold Levinson, M.D., on December 14, 2020. (ECF No. 59; Ex. G-H.) Petitioner filed a responsive expert report by Dr. Axelrod in March of 2021. (ECF No. 62; Ex. 62.)

During a status conference held June 9, 2021, petitioner's counsel advised that Dr. Stark was unable to participate in the upcoming entitlement hearing for medical reasons. (EF No. 80.) The hearing was cancelled. (*Id*.) Due to the cancellation of the hearing, Special Master Oler ordered the parties to file further expert reports addressing specific questions. (ECF No. 82.) Respondent filed responsive reports by Drs. Levinson and LaRue (ECF No. 84; Exs. I-J) and petitioner filed a report by Dr. Axelrod. (ECF No. 83; Ex. 73-78.[2]) However, petitioner's counsel advised that Dr. Stark's medical condition prevented him from providing a further report and petitioner was instructed to retain a different cardiologist. (Scheduling Order (Non-PDF), 8/25/2021.) Petitioner subsequently filed a report by cardiologist Athol Winston Morgan, M.D., on January 6, 2022. (ECF No. 86; Ex. 80-81.)

On February 1, 2022, respondent filed a joint status report on behalf of the parties indicating that the parties agree the record of the case is complete. (ECF No. 88.) Shortly thereafter, the case was reassigned to the undersigned on February 7, 2022. (ECF No. 90.) I ordered the parties to file a joint status report proposing a mutually agreeable briefing schedule for a ruling on the written record or otherwise advising how they wish to proceed. (Scheduling Order (Non-PDF), 2/8/2022.) In response, the parties proposed a briefing schedule. (ECF No. 91.) Petitioner filed a motion for a decision on the record on April 14, 2022. (ECF No. 92.) Respondent filed his response on June 15, 2022. (ECF No. 94.) Petitioner filed her reply on July 17, 2022. (ECF No. 96.)

[2] Exhibit designations 63-72 were used for the filing of highlighted literature responsive to the prehearing order. This was also the first time petitioner filed articles designated as citations from Dr. Stark's reports (ECF No. 66), though much of the same literature had already been filed in in connection with other experts' reports.

This case is now ripe for resolution. I have concluded that the parties have had a full and fair opportunity to develop the record and that it is appropriate to resolve this case without an entitlement hearing. S*ee Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs*., 671 F.3d 1368, 1385 (Fed. Cir. 2012); *Jay v. Sec'y of Dept. of Health & Human Servs.*, 998 F.2d 979, 983 (Fed. Cir. 1993.)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2).

III. Factual History

a. As reflected in the medical records

i. Pre-vaccination

Petitioner was 45 years old when she received a flu vaccination on October 26, 2016. (Ex. 2.) Prior to her vaccination, petitioner had no history of heart or respiratory disease. (Ex. 3, p. 2 (review of symptoms notes "no chest pain, PND, orthopnea, or edema" and "no dyspnea, cough, hemoptysis, or pleuric pain").) Petitioner's earliest available record is from a visit with Dr. Jeffrey Glickman to establish care on May 16, 2014. (*Id.* at 1.) Her chief complaints at this visit were elevated blood pressure and a recent onset of extreme fatigue. (*Id.*) Petitioner's past medical history included migraine headaches. (*Id.*) Dr. Glickman diagnosed petitioner with hypertension due to an underlying health condition or possibly due to lifestyle.[3] (*Id.* at 4.) Petitioner had a follow-up appointment with Dr. Glickman on June 20, 2014, where he noted petitioner's weight and blood pressure had both decreased and nasal Imitrex was helping with the migraines. (*Id.* at 5.)

Petitioner saw neurologist, Dr. Daniela Saadia, on March 25, 2015, with a chief complaint of migraine headaches. (Ex. 24, p.1.) Dr. Saadia noted petitioner's migraines began at age 20 and had increased in frequency to "12 headache days a month." (*Id.*) Dr. Saadia prescribed nasal Imitrex and Topomax. (*Id.*)

Petitioner presented to the Martin Memorial Hospital ER on April 4, 2015, with chief complaints of cough, body aches, and sore throat. (Ex. 9, p 2.) Petitioner's flu test was positive for Influenza B. (*Id.*) Petitioner followed up with Dr. Glickman on April 15, 2015, who noted petitioner "went to the emergency room complaining of cough sore throat and muscle aches" and "tested positive for influenza B by nasal swab." (Ex. 3, p. 7.)

On October 9, 2015, petitioner saw Dr. Saadia for migraine follow-up. Dr. Saadia noted petitioner's headaches had increased in frequency and duration and diagnosed petitioner with migraine without aura. (Ex. 24, p. 5.) On October 16, 2015, petitioner received a brain MRI. (*Id.* at 8.) The impression was "minimal asymmetry of the left side of the pituitary gland," but otherwise within normal limits. (*Id.*)

[3] Dr. Glickman noted petitioner "freely admits to eating excessive salt-containing foods." (Ex. 1, p.1.) She had also gained 20 pounds over the preceding year. (*Id.* at 4.)

Petitioner had an appointment with Dr. Glickman for her six-month follow-up on October 21, 2015, where he noted her migraine symptoms were "[s]evere headache starting over the right eye progressing to the back of the skull associated with nausea and light intolerance." (Ex. 3, p. 11.) His diagnosis is intractable chronic migraine without aura and without status migrainosus. (*Id*.) Dr. Glickman notes that petitioner's elevated blood pressure had improved when she lost some weight. (*Id*.) Petitioner also received a flu vaccination during this visit. (*Id.* at 13; Ex. 2, p. 1.)

On November 9, 2015, petitioner saw Allan Loesch, PA-C, for injuries she sustained in a motor vehicle collision that occurred on November 1, 2015. (Ex. 11, p. 1.) Mr. Loesch's diagnosis was left scapular pain and left thoracic and lumbar pain without radiculopathy. (*Id.*) Petitioner had an MRI of her back performed on March 6, 2016. (Ex. 10, p. 5.)

Petitioner's next follow-up with Dr. Glickman was on April 6, 2016. (Ex. 3, p. 14.) He noted petitioner had "tolerated her influenza vaccine without any difficulty." (*Id*.) He also recorded petitioner's back pain due to the motor vehicle accident and that she was being treated by a chiropractor and spine surgeon for a herniated disc. (*Id.*) Petitioner's migraine headaches were "severe and occur almost daily without aura" and she requested a referral to another neurologist. (*Id*.)

On July 1, 2016, petitioner was seen at Coastal Orthopaedic & Sports Medicine for left shoulder pain and was diagnosed with bicipital tendinitis. (Ex. 7, p. 9.)

Petitioner saw Candy Jones, ARNP, for a neurological evaluation of her migraine headaches on July 11, 2016. (Ex. 20, p. 1.) Ms. Jones noted petitioner's migraines averaged four days in duration with nausea on the third day and would usually go away with Imitrex nasal spray. (*Id.*) At a follow-up visit on November 17, 2016, Ms. Jones recorded that petitioner's headaches had begun waking her up in the middle of the night and petitioner reported experiencing a mild headache every day with possible triggers then worsening the headache. (*Id.* at 5.)

Petitioner's next follow-up with Dr. Glickman occurred on October 26, 2016, at which time she received the influenza vaccination at issue. (Ex. 2, p. 1; Ex. 3, p. 16.) Dr. Glickman noted petitioner had begun taking nortriptyline for her "severe recurrent migraines." (Ex. 3, p. 17.) He also recorded petitioner's history of facet injections and a recent rhizotomy to treat bursitis tendinitis and bone spur in her left shoulder. (*Id.*) Petitioner's blood pressure was 130/82 and Dr. Glickman noted she had "no cardiac [or] pulmonary … symptoms. (*Id*.)

ii. Post-vaccination

Petitioner presented to the St. Lucie Medical Center ER at just before midnight on October 27, 2016, with chief complaints of chest pain, diaphoresis, and nausea. (Ex. 4, p. 13.) Petitioner described "10/10 chest pain that awoke her from sleep." (*Id.*) Her vital signs included a blood pressure of 147/103; a body temperature of 99.0 degrees Fahrenheit; and a pulse of 113 beats per minute. (*Id.* at 15.) A portable x-ray of her

chest was negative. (*Id.* at 18.) On physical exam, petitioner's cardiovascular symptoms were "irregularly irregular, tachycardic." (*Id.*at 16.)

Petitioner had an abnormal EKG at 11:32 pm, that showed acute myocardial infarction ("MI"). (*Id.* at 52.) Specifically, the EKG demonstrated "[a]trial fibrillation with rapid ventricular response with premature ventricular or aberrantly conducted complexes"; "[l]ow voltage QRS; [p]ossible Inferior infarct, age undetermined"; and "[a]nteroseptal infarct, possibly acute." Petitioner had a second EKG at 11:41 pm, which demonstrated "[s]inus tachycardia"; "[r]ight superior axis deviation"; and "low voltage QRS." (*Id.*) This EKG noted the inferior and anterior infarcts cited on the previous EKG and was similarly flagged with "Abnormal EKG" and "ACUTE MI." (*Id.*) It also noted that when compared to the previous EKG: "Sinus rhythm has replaced Atrial Fibrillation." (*Id.*)

A re-evaluation noted that petitioner lost consciousness and CPR was initiated. (*Id.* at 19.) Petitioner underwent defibrillation twice at 200 joules and then once at 300 joules, after which her atrial fibrillation was successfully converted to sinus rhythm. (*Id.* at 19, 54.) Petitioner's lab work revealed an elevated white blood cell (WBC) count of 11.2 (normal range 3.6-11.0). (*Id.* at 18.)

St. Lucie Medical Center arranged to have petitioner transferred to Lawnwood Regional Medical Center ("LRMC") for a cardiac catheterization. (Ex. 4, p. 19.) Petitioner's condition at discharge was listed as critical, but stable for transfer. (*Id.* at 19-20.) The clinical impression of her visit included a primary impression of "ST elevation myocardial infarction (STEMI) of anterior wall" and secondary impressions of "[a]trial fibrillation with RVR, [c]ardiac arrest," and "[v]entricular tachycardia." (*Id.* at 20.)

On October 28, 2016, Petitioner was admitted to LRMC and Dr. Anthony Lewis immediately performed a cardiac catheterization. (Ex. 5, p. 5; Ex. 8, p. 56.) The indication for the catheterization listed "[a]cute coronary syndrome with STEMI" and "chest pain and back pain." (*Id.*) Dr. Lewis found no "critical disease" in the left main artery, left anterior descending artery, circumflex artery, or right coronary artery. (*Id. See also* Ex. 8 at 56 ("It appears that there are no coronary findings on cath.").) He noted that the absence of critical disease in the right coronary artery presented a "coronary enigma" because petitioner "absolutely had damage to her apex" and "[t]here was also reported shock x2." (*Id.*) Dr. Lewis found no evidence of occlusion of petitioner's left anterior descending artery in the pictures. (*Id.*) Dr. Heitman reviewed the pictures and confirmed "there is no significant coronary disease seen." (*Id.*) Dr. Lewis stated that petitioner would need an electrophysiology study if no dilatable artery could be found because "she did call twice and she complained of back pain." (*Id.*)

After the catheterization, petitioner underwent a transthoracic echocardiogram. (*Id.* at 8.) The summary indicated a mild to moderate reduction in systolic function; an ejection fraction of 45-50%; and diffuse hypokinesis. (*Id.*) Mild to moderate regurgitation was observed in petitioner's tricuspid and pulmonic valves. (*Id.*)

On the afternoon of October 28, 2016, the petitioner underwent a computerized tomography ("CT") scan. (Ex. 8, p. 290.) The impression stated "[n]o pulmonary embolism evident" and "[a]typical bilateral pulmonary infiltrates. Vascular congestion versus viral/infectious pneumonitis." (*Id.*) The next day, a portable radiograph of petitioner's chest found "vascular interstitial markings appear more prominent compared to the previous study consistent with an element of mild fluid overload." (*Id.* at 291.)

On October 29, 2016, Dr. Lewis evaluated petitioner and determined she would need a stress test and electrophysiologic studies before discharge. (*Id.* at 75.) He also stated, "CAD with 90% LAD but very small vessel doubt this is reasonable for SCD." (*Id.* at 76.) Petitioner's WBC had increased to 25.4 (normal range 3.6-11.0). (*Id.* at 123.) Dr. Dragana Orlovic was consulted to rule out endocarditis and leukocytosis as potential causes of petitioner's chest pain. (*Id.* at 56). In petitioner's history of present illness, Dr. Orlovic wrote that petitioner "had history of flu vaccine, which she received a couple of days ago. That same night she developed local reaction with redness and some skin changes. The next day, this had resolved. She had flu vaccine in the past and did not have any reaction to them." (*Id.*) Dr. Orlovic's differential diagnosis included "vascular congestion, viral or infection pneumonitis." (*Id.*)

On October 31, 2016, petitioner had a Myocardial SPECT test. (*Id.* at 292.) The impression was "[l]arge defects involving the apex, inferoseptal and anteroseptal walls compatible with multivessel disease." (*Id.*) Dr. Lewis evaluated petitioner again that day and noted petitioner's small left ascending artery and the presence of coronary artery disease did not explain all of petitioner's clinical course. (*Id.* at 69.) Petitioner's WBC had decreased but was still elevated at 15.3 (normal range 3.6-11.0). (*Id.* at 19.)

Petitioner was discharged from LRMC and admitted to JFK Medical Center on November 2, 2016. (*Id.* at 19; Ex. 6, p, 2.) Her assessment at discharge listed her previous diagnoses and included "s/p [status post] flu shot reaction." (Ex. 8 at 18.)

Dr. Jeffrey Devon attended to petitioner on November 2, 2016. (Ex. 6, p. 12.) His impression noted petitioner had history of "diffuse and transient" ST-elevation; "normal epicardial arteries as well as coronaries"; "infiltrates in her lung which may be viral"; and "no fever." (*Id.* at 13.) Dr. Devon's plan included placing an implantable cardioverter-defibrillator ("ICD") the next morning and having petitioner evaluated by infectious disease and rheumatology. (*Id.*)

On November 2, 2016, Dr. Ana Raquel Mateo-Bibeau was asked to consult on petitioner's case to investigate "possible myocarditis," and to rule out infection. (Ex. 6, p. 26.) Dr. Mateo-Bibeau noted that petitioner reported getting the seasonal flu vaccine on October 26, 2016; was feeling "run down" within 24 hours and woke up with severe, sharp chest pain, shortness of breath, and bilateral tingling and numbness in her hands. (*Id.*) Dr. Mateo-Bibeau cleared petitioner for surgery to place the ICD. (*Id.*)

On November 3, 2016, petitioner received an ICD. (*Id.* at 135.) Petitioner also underwent a cardiac MRI. (Ex. 22, p. 1.) The MRI impression showed an ejection fraction of 53%; "[t]ransmural anterior infarct in mid LAD territory with associated

akinesis"; "[m]ural thrombus adjacent to LAD infarct"; and "[s]mall to moderate pericardial effusion."

Petitioner was discharged in stable condition from JFK Medical Center to her home on November 4, 2016. (Ex. 6, p. 11.) Discharge instructions indicated petitioner could resume previous diet or begin a "Cardiac/Healthy Heart" diet and could resume previous activity "as tolerated." (*Id.*)

On November 28, 2016, Petitioner visited spine surgeon Dr. Thomas Roush for follow-up on a rhizotomy performed on September 16, 2016, for mid-back pain. (Ex. 12, p. 12.) Petitioner reported the rhizotomy improved her mid-back pain. (*Id.*) Dr. Roush noted petitioner's recent hospitalization due to heart attack and subsequent placement of a defibrillator. (*Id.*)

On December 2, 2023, petitioner saw Dr. Lewis to establish care and for an initial evaluation of palpitations that developed acutely after her ICD was implanted. (Ex. 5, p. 1.) Dr. Lewis diagnosed petitioner with unstable angina and counseled her to control her blood pressure, limit sodium, and improve her diet and exercise.[4] (*Id.* at 3.)

Petitioner followed up with Dr. Glickman on December 9, 2016. (Ex. 3, p. 20.) At this visit, petitioner complained of arm discomfort in her left arm and Dr. Glickman noted her arm was in a sling for four weeks due to defibrillator placement. (*Id.*) Dr. Glickman recorded that petitioner's blood pressure had been low and she was symptomatic. (*Id.* at 22.) He advised her to hold off taking lisinopril if her systolic blood pressure was below 110 and to go over this with her cardiologist at her appointment the following week. (*Id.*) Dr. Glickman remarked "[i]t is quite interesting that since her event she no longer has hypertension and has had no migraines." (*Id.*)

On March 2, 2017, petitioner saw Dr. Lewis for her 3 month follow up. (Ex. 19, p. 1.) She complained of daily mild headaches, difficulty sleeping, and diaphoresis. (*Id.*) She also reported fluttering in her chest which caused shortness of breath. (*Id.*) Dr. Lewis diagnosed petitioner with unstable angina and ordered an EKG. (*Id.* at 1-2.)

Petitioner saw Dr. Glickman for a routine check-up on May 26, 2017. (Ex. 3 at 23.) Dr. Glickman noted the pain and restriction in petitioner's left shoulder due to implant placement had improved by 90%. (*Id.*) He also noted that petitioner's defibrillator had been interrogated with no serious arrhythmias found. (*Id.* at 24.) Petitioner reported her migraines had returned and Dr. Glickman remarked the frequency had decreased to "only 5 in the last 6 months." (*Id.*)

On August 10, 2017, petitioner presented to the St. Lucie Medical Center emergency room and was admitted to the hospital after being diagnosed with gallstones. (Ex. 14, p. 2.) She was discharged home on August 12, 2017. (*Id.* at 9.)

[4] The record also indicates that Dr. Lewis counseled petitioner to quit smoking, but this appears to be included in error. In the same visit, Dr. Lewis records "Smoking status: nonsmoker" under the heading "HPI" and "Never smoker" under the heading "Social History." (Ex. 5, p. 1). Petitioner avers that she has never been a smoker. (Ex. 1.)

On August 22, 2017, petitioner followed up with a nurse practitioner, who referred her for an esophagogastroduodenoscopy. (Ex. 13, p. 15.)

Petitioner returned to Dr. Lewis on August 28, 2017. (Ex. 19, p. 3.) Petitioner reported continued fluttering in her chest. (*Id.*) Dr. Lewis' diagnosis remained unstable angina and he ordered another EKG. (*Id.* at 3-4.)

Petitioner had a positive flu test and was treated at an urgent care clinic on November 25, 2017. (Ex. 18, pp. 1-3.)

Petitioner's next follow-up appointment with Dr. Lewis was on January 4, 2018. (Ex. 19, p. 5.) Her diagnosis of unstable angina remained unchanged. (*Id.* at 6.) Dr. Lewis' physician assistant provided petitioner with a flu vaccine exemption letter. (Ex. 59, p. 2.)

Petitioner visited a new cardiologist, Dr. Darryl Miller, on January 11, 2019. (Ex. 27, p. 1.) Dr. Miller noted "[i]t is very likely [petitioner's] cardiac event in 2016 was Takotsubo syndrome, however her wall motion appears to have not recovered. The precipitating event is unclear, however appears to be related to the influenza vaccine." (*Id.*)

On April 4, 2018, petitioner followed up with nurse practitioner Candy Jones. (Ex. 20, p.10.) Ms. Jones noted petitioner "[a]pparently had MI due to flu shot 2016." (*Id.*) Petitioner reported she didn't feel her headaches were as frequent but were more intense. (*Id.*)

Petitioner presented to the St. Lucie Medical Center emergency room on February 14, 2020, for a defibrillator dysfunction. (Ex. 60, p.1.) The records state petitioner "was catheterized after the STEMI which was thought to be due to influenza vaccine reaction secondary to no coronary artery occlusion." (*Id.*) Another record entry states, "defibrillator put in 3 years ago after reaction to flu shot went into cardiac arrest per patient." (Ex. 61, p. 425.)

b. As reflected in petitioner's affidavit

Petitioner indicates that she considered herself a healthy woman prior to vaccination, with no history of heart or breathing problems. She was not a smoker. (Ex. 1, p. 1.) She indicates that after receiving the vaccination at issue, she "began to experience most of the symptoms that were listed on [the] vaccination side effects sheet they gave me, swelling, hives, headache, arm pain." She took Benadryl and went to work the next day. (*Id*.) At about 11:00 PM on October 27, 2016, she awoke with chest pains as well as numbness and tingling in her arms and hand. She went to the emergency department. (*Id*. at 1-2.) Thereafter, petitioner describes the course of her treatment, including implantation of her defibrillator and attendant shoulder pain. (*Id*. at 2-3.)

Petitioner relates that "[t]he doctors have told my husband and I that my heart attack resulted in myocardial necrosis. I am now faced with the reality of my new life,

one that requires constant vigilance on my part to avoid magnetic fields, overexertion, anxiety and stress along with diet and my overall health." Petitioner indicates she had to quit her job as a result. (*Id*. at 3.)

IV. Summary of Expert Opinions

a. Petitioner's experts

i. Robert Stark, M.D. (cardiology)[5]

Dr. Stark opines that petitioner suffered an acute myocardial infarction involving two separate areas of her heart, the anterior wall and infero-apical wall, which are supplied by the left anterior descending and right coronary arteries respectively. (Ex. 25, p. 3.) This occurred despite both arteries being free of any atherosclerotic plaque (*i.e*., cholesterol blockage). Thus, Dr. Stark explains petitioner's treating cardiologist indicated that petitioner suffered coronary enigma with no evidence of occlusion. (*Id*.) Dr. Stark suggests that the only explanation for such an occurrence is systemic inflammation affecting the coronary arteries. (*Id.*) He suggests that petitioner's exaggerated immune response to vaccination the day prior, evidenced by her arm swelling, headaches, pain, and malaise, favors this explanation. (*Id*.) Further to this, Dr. Stark attributes petitioner's elevated white blood cell count to this inflammation rather than any incurrent viral infection. (*Id*.) Additionally, he suggests that the fact that multiple regions of the heart were damaged is evidence the root cause was systemic rather than any simple mechanical blockage. (*Id*. at 4.) Dr. Stark cites four articles for the proposition that the flu vaccine can cause an acute phase inflammatory response affecting the coronary arteries (Carty et al., Glaser, et al., Liuba, et al., and Ritter, et al.).[6] (*Id*. at 3.)

Dr. Stark characterizes Dr. LaRue's competing explanation (discussed separately below) as constituting "a very unlikely series of occurrences," namely an acute

[5] As of the date of his curriculum vitae, Dr. Stark was an Adjunct Assistant Professor of Medicine at New York Medical College and an Attending Physician in Internal Medicine and Cardiology at Greenwich Hospital in Connecticut. (Ex. 26, p. 1.) He received his bachelor's degree from the University of Michigan and his Doctor of Medicine from Harvard Medical School. (*Id.*) He is licensed to practice medicine in New York and Connecticut. (*Id.* at 1-2.) Dr. Stark is board certified by the American Board of Internal Medicine with a subspecialty in cardiovascular disease. (*Id.* at 2.) In addition, he authored 16 peer-reviewed articles. (*Id.* at 3-4.)

[6] Cara L. Carty et al., *Inflammatory Response After Influenza Vaccination in Men with and without Carotid Artery Disease*, 26 ARTERIOSCLEROSIS THROMBOSIS & VASCULAR BIOL 2738 (2006) (Ex. 67); Ronald Glaser et al., *Mild Depressive Symptoms Are Associated with Amplified and Prolonged Inflammatory Responses After Influenza Virus Vaccination in Older Adults*, 60 ARCH GEN PSYCHIATRY 1009 (2003) (Ex. 68); Petru Liuba et al., *Residual Adverse Changes in Arterial Endothelial Function and LDL Oxidation After a Mild Systemic Inflammation Induced by Influenza Vaccination*, 39 ANNALS OF MEDICINE 392 (2007) (Ex. 69); O. Ritter et al., *Myocardial Infarction After Influenza Vaccination*, 92 Z CARDIO 962 (2003) (Ex. 71). The Liuba et al. article was additionally filed as Ex. 46 and all four articles were additional filed as Tabs 15-18 of respondent's Ex. C.

formation of coronary plaque which then ruptures to cause myocardial infarction and then undergoes positive remodeling to leave no trace of any coronary lesion by the time of petitioner's cardiac catheterization just hours later. (Ex. 28, p. 1.) Dr. Stark stresses Dr. Rose's agreement that inflammation can occur within hours of a stimulus to assert that this is what happened in petitioner's case. (*Id*. at 2.)

Dr. Stark was also prompted to answer two follow-up questions. First, what would he expect to see if the series of events described by Dr. LaRue took place and, second, what is the significance of the preponderance of neutrophils in petitioner's white blood cell count. (ECF No. 41.) Regarding the first question, Dr. Stark disputes that the type of "positive remodeling" hypothesized by Dr. LaRue could occur within a few hours, but indicates that if it did occur, then one would expect to see dilation or enlargement of the coronary artery where the remodeling took place as well as remanent evidence of the coronary plaque that had ruptured. He notes this was not seen on the October 28, 2015, catheterization films. (Ex. 58, pp. 1-2.) Regarding the second question, Dr. Stark opines that the preponderance of neutrophils and paucity of lymphocytes indicates either systemic inflammation or bacterial infection to the exclusion of a viral infection. (*Id*. at 2.)

ii. Athol Winston Morgan (cardiology)[7]

Dr. Morgan was presented to respond to specific questions posed by the special master after Dr. Stark became unavailable. (Ex. 80.)

Dr. Morgan was asked to respond to Dr. LaRue's statement that "although there was some suggestion of inferior-septal involvement on the presenting ECG and nuclear medicine scan, the cardiac MRI ultimately showed damage only to the anterior wall of the heart, which falls within the LAD territory." (Ex. 80, p. 1.) He explained that myocardial infarction is "dynamic" and the process time dependent. (*Id.*) Tissue that is deprived of oxygen for a shorter amount of time may only be transiently ischemic, which is referred to as myocardial "stunning." (*Id.*) He opines that the expected area of dysfunction may shrink over time and therefore, it is likely that petitioner's earlier ECG and nuclear scan showed a more extensive area of injury while the later MRI likely reflected a degree of recovery in the inferior-septal region. (*Id*. at 1-2.)

Asked why Dr. Stark believes petitioner's leukocyte/lymphocyte count supports inflammation rather than intercurrent viral infection, Dr. Morgan explained that Dr. Stark is of the view that viral infections precipitate an immune response involving more

[7] Dr. Morgan is an Adjunct Assistant Professor of Medicine at the University of Maryland School of Medicine and an Instructor at Johns Hopkins University School of Medicine. (Ex. 81, p. 2.) He is the Director of the Division of Cardiology at Grace Medical Center and the CEO and Medical Director of One Heart, LLC. (*Id.*) Dr. Morgan received his bachelor's degree from Columbia College and his Doctor of Medicine from Johns Hopkins University School of Medicine. (*Id.* at 1.) He also received his Master of Health Science from Johns Hopkins School of Hygiene and Public Health. (*Id.*) Dr. Morgan is currently licensed to practice medicine in Maryland and is board certified in Internal Medicine and Cardiovascular Disease by the American Board of Internal Medicine. (*Id.* at 2.) In addition, Dr. Morgan has been the principal investigator in 13 clinical trials. (*Id.* at 4.)

lymphocytes and fewer leukocytes. (Ex. 80, p. 2.) Dr. Morgan likewise endorses that view. (*Id*.)

Asked whether the anterior wall and the infero-apical wall cited by Dr. Stark are supplied by two separate coronary arteries, Dr. Morgan indicated that coronary anatomy is "quite variable" among individuals. (*Id*. at 2.) The anterior wall is predominantly supplied by the left anterior descending ("LAD") coronary artery. (*Id.*) The inferior wall is predominantly supplied by the right coronary artery ("RCA"). (*Id.*) The infero-apical, is a "watershed area" that might be supplied by either the LAD or RCA depending on the individual. (*Id*.) (Dr. Morgan provided a diagram at the request of the special master.)

Asked whether systemic inflammation can affect cardiac autonomic function, Dr. Morgan indicates that it can. (*Id.* at 2.) He specifies that petitioner's "vigorous acute phase immune response" to vaccination "can precipitate a variety of deleterious cardiac effects, including vasospasm, myocarditis, endothelial dysfunction or endothelial injury leading to myocardial infarction, potential lethal arrythmias, and autonomic dysfunction." (*Id*. at 2.)

Asked whether it is significant that petitioner had atherosclerotic disease in her small diagonal artery, Dr. Morgan appears to suggest that this may be irrelevant to either Dr. Stark's or Dr. Axelrod's theories, but that it supports a third theory of causation. (*Id*. at 2.) He opines that "the inflammatory response precipitated endothelial injury leading to clot formation and ultimately occlusion of the artery causing myocardial infarction. (*Id.* at 3.) The clot then dissolved and moved downstream and, as such, was not visible at the time of the cardiac catheterization." (*Id*.)

Asked whether a systemic reaction can precipitate Takotsubo syndrome (a condition raised by treating physician, Dr. Miller), Dr. Morgan indicates that it can. (*Id.*) However, he does not agree that petitioner suffered Takotsubo syndrome. (*Id*.) Takotsubo syndrome is usually benign, resulting in full recovery of myocardial function within days. (*Id*.)

Asked whether 31 hours post-trigger is an appropriate timeframe for a systemic inflammatory response to occur, Dr. Morgan indicates that he agrees with Dr. Axelrod that the immune response can peak at 24 hours and persist for some time. (*Id.*) He opines that 31 hours is "absolutely" within the appropriate timeframe for such a reaction to occur. (*Id*.)

iii. David Axelrod, M.D. (immunology)[8]

Dr. Axelrod cites three studies (by Fagnoul, et al., Paddock, et al., and Fountoulaki, et al.)[9] that he indicates show that a subset of patients suffering influenza *infection* experience myocardial damage and cardiovascular events. (Ex. 29, p. 2.) Initially, he cites a further study by Rasmussen, et al.,[10] which he indicates shows subjects experiencing elevations in certain cytokines following subarachnoid hemorrhage and vasospasm, though vasospasm alone was not associated with increased cytokine levels. (*Id*. at 3.) However, he also cites three additional studies (by Fassbender et al., Li, et al., and Bowman, et al.)[11] that he asserts show vasospasm to be associated with elevated IL-6, which he opines evidence IL-6 as a significant cause of vasospasm. (*Id*. at 4.) In any event, Dr. Axelrod indicates the cytokine levels observed by Rasmussen, et al., were lower than the levels observed in a study by Kashiwagi, et al.,[12] which observed post-vaccination cytokine responses. (*Id*.) He cites three further studies (by Sawurwein-Teisssel, et al., Christian, et al., and Nakayama, et al.)[13] that he indicates show elevated cytokines post-flu vaccination (specifically TNF-α,

[8] Dr. Axelrod currently works for Allergy & Asthma Consultants, Inc. (Ex. 30, p. 2.) He received his bachelor's degree, master's degree, and Doctor of Medicine from the University of Michigan. (*Id.*) Dr. Axelrod is currently licensed to practice medicine in Michigan, Pennsylvania, and New Jersey. (*Id.* at 3.) He is board certified in Internal Medicine and Rheumatology by the American Board of Internal Medicine. (*Id.*) He is also certified by the Association of American Laboratory Immunologists and the American Board of Allergy and Immunology. (*Id.*) In addition, Dr. Axelrod has authored 13 peer-reviewed articles.

[9] David Fagnoul et al*., Myocardial Dysfunction During H1N1 Influenza Infection*, 28 J OF CRITICAL CARE 321 (2013) (Ex. 33); Christopher D. Paddock et al., *Myocardial Injury and Bacterial Pneumonia Contribute to the Pathogenesis of Fatal Influenza B Virus Infection*, 205 J OF INFECTIOUS DISEASE 895 (2012) (Ex. 34); Katerina Fountoulaki et al., *Beneficial Effects of Vaccination on Cardiovascular Events: Myocardial Infarction, Stroke, Heart Failure*, 141 CARDIOLOGY 98 (2018) (Ex. 35). The Fountoulaki et al. article was additionally filed as Ex. C, Tab 4.

[10] Rune Rasmussen et al., *Plasma Levels of IL-6, IL-8, IL-10, ICAM-1, VCAM-1, IFNg, and TNFa are not Associated with Delayed Cerebral Ischemia, Cerebral Vasospasm, or Clinical Outcome in Patients with Subarachnoid Hemorrhage,* 128 WORLD NEUROSURGERY E1131 (2019) (Ex. 36).

[11] K. Fassbender et al., *Inflammatory Cytokines in Subarachnoid Haemorrhage: Association With Abnormal Blood Flow Velocities in Basal Cerebral Arteries*, 70 J NEUROL NEUROSURG PSYCHIATRY 534 (2001) (Ex. 43); Jian-Jun Li et al., *Increased Peripheral Circulating Inflammatory Cells and Plasma Inflammatory Markers in Patients with Variant Angina*, 19 CORONARY ARTERY DISEASE 293 (2008) (Ex. 44); George Bowman et al., *Neutralizing Antibody Against Interleukin-6 Attenuates Posthemorrhagic Vasospasm in the Rat Femoral Artery Model*, 54 NEUROSURGERY 719 (2004) (Ex. 45). The Bowman et al. article was additionally filed as Ex. 63.

[12] Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 HUM VACCINES & IMMUNOTHERAPEUTICS 677 (2014) (Ex. 39). This article was additionally filed as Ex. 77.

[13] M. Saurwein-Teisssel, et al., *Whole Virus Influenza Vaccine Activates Dendritic Cells (DC) and Stimulates Cytokine Production by Peripheral Blood Mononuclear Cells (PBMC) While Subunit Vaccines Support T Cell Proliferatio*n, 114 CLINICAL & EXPERIMENTAL IMMUNOLOGY 271 (1998) (Ex. 37); Lisa M. Christian, et al., *Serum Proinflammatory Cytokine Responses to Influenza Virus Vaccine among Women during Pregnancy versus Non-Pregnancy*, AM J REPRODUCTIVE IMMUNOLOGY 1 (2013) (Ex. 38); Tetsuo Nakayama, et al., *Alum-Adjuvanted H5N1 Whole Virion Inactivated Vaccine (WIV) Enhanced*

IL-2, IL-6, and IFN- γ). (*Id*.) A murine model by Gardiner, et al.,[14] further produced increased heart rate and decreased arterial pressure by infusing TNF-α and IL-1β. (*Id*. at 3-4.) Finally, Liuba, et al., showed that elevated proinflammatory cytokine markers precede onset of myocardial infarction and may be predisposing. The risk existed regardless of fever. (*Id*. (discussing Liuba, et al., *supra* n. 6, at Ex. 69).)

Dr. Axelrod notes that Kashiwagi, et al., and Christian, et al., showed that cytokine levels peak by about 24 hours post-vaccination and then persist "for some time." (*Id.* at 5.) He opines the timing of petitioner's cardiac event, occurring about 31-32 hours post-vaccination, is consistent with this timeframe. (*Id*.) Dr. Axelrod opines that petitioner "experienced elevated temperature, vasospasm with tissue death and dysfunction (myocardial infarction and cardiac dysrhythmia), as can be seen with cerebrovascular vasospasm mediated brain damage, following cytokine elevations, following subarachnoid hemorrhage." (*Id.*) He suggests that no other cause of inflammation is evidenced apart from vaccination. (*Id*.) In his second report, Dr. Axelrod further suggests in response to Dr. Levinson that petitioner's history of migraine disorder predisposed her to vasospastic disease and myocardial infarction. (Ex. 62, pp. 1-2.[15]) Dr. Axelrod is critical of the epidemiologic studies first cited by Dr. Rose and referenced again by Dr. Levinson. (Ex. 29, pp. 6-7; Ex. 62, pp. 2-4.) Among other limitations, he notes in particular that several of these studies found a cardioprotective effect of flu vaccination among those who had prior cardiovascular disease, which would not include this petitioner. (*Id.*)

Dr. Axelrod's third report answered specific questions posed by the special master. (Ex. 73, p. 1.) Asked if administration of methylprednisolone and prednisone could have caused petitioner's elevated white blood cell count, Dr. Axelrod agrees that the corticosteroids administered to petitioner were the cause of her elevated white blood cell count. (*Id*. at 1-2.) Responding to the question of whether the timing is appropriate in this case, Dr. Axelrod reiterated that his theory anticipates a peak cytokine response around 24 hours and persisting. (*Id*. at 2.) Responding to the question of whether systemic inflammation can affect cardiac autonomic function, Dr. Axelrod cites a study by McElhaney, et al.,[16] which he indicates shows the flu vaccine to elevate IL-2, and a

Inflammatory Cytokine Productions, 30 VACCINE 3885 (2012) (EX. 40). The Christian et al. article was additionally filed as Ex. G, Tab 1.

[14] S.M. Gardiner et al., *The Influence of Antibodies to TNF-a and IL-1b on Haemodynamic Responses to the Cytokines, and to Lipopolysaccharide, in Conscious Rats*, 125 BRITISH J OF PHARMACOLOGY 1543 (1998) (EX. 41).

[15] Citing Simona Sacco, et al., *EHMTI-0392. Migraine and Risk of Ischemic Heart Disease: A Systematic Review and Meta-Analysis of Observational Studies*, 15 J OF HEADACHE AND PAIN 1 (2014) (EX. 65) and Ayesha Saeed, et al., *Association of Migraine and Ischemic Heart Disease: A Review*, 11 CUREUS 1 (2019) (Ex. 66).

[16] Janet E. McElhaney, et al., *The Effect of Influenza Vaccination on IL2 Production in Healthy Elderly: Implications for Current Vaccination Practices*, 47 J OF GERONTOLOGY M3 (1992) (EX. 79).

study by Guinjoan, et al.,[17] which he indicates shows elevated IL-2 affecting autonomic neuron discharge, increasing sympathetic output and decreasing parasympathetic thoracic activity. (*Id*. at 2.)

b. Respondent's experts

i. Shane Larue, M.D. (cardiology)[18]

Dr. LaRue opines that petitioner's cardiac event is best described as myocardial infarction with no obstructive coronary atherosclerosis ("MINOCA"). (Ex. A, p. 5.) This is a syndrome characterized by clinical evidence of myocardial infarction with normal or near-normal coronary arteries. (*Id*.) Causes of MINOCA include coronary artery vasospasm, eccentric coronary plaque, Takotsubo syndrome, microvascular spasms, myocarditis, and coronary embolism. (*Id*.) Of these causes, Dr. LaRue finds eccentric coronary plaque (with positive remodeling) or Takotsubo syndrome to be more likely. (*Id.*) Petitioner fits the profile for Takotsubo syndrome in several ways and it is associated with migraine headaches; however, although it remains a "reasonable possibility," it is less likely because petitioner's cardiac MRI demonstrated a transmural infarct localized to the ALD territory and she had substantial troponin elevation, higher than would typically be seen with Takotsubo syndrome. (*Id*. at 5-6.) Thus, Dr. LaRue opines that the most likely explanation for petitioner's MINOCA is positive remodeling (eccentric plaque disruption). He explains that "[t]his clinical entity can present with chest pain, ST segment elevation on ECG, elevated troponin values, and no obstructive disease visible on coronary angiography. Additionally, patients with [myocardial infarction] related to no obstructive coronary atherosclerosis can demonstrate ischemia and infarction on cardiac MRI, as was the case for [petitioner]." (*Id*. at 6.) Petitioner's ventricular fibrillation arrest was a result of her MINOCA. (*Id.*)

Regarding Dr. Stark's assertion that two areas of the heart were affected, Dr. LaRue raises two points.[19] First, he explains that in some people the LAD can supply both the anterior and infero-apical walls. (*Id*. at 7.) With regard to whether this is the

[17] Salvador M. Guinjoan, et al., *Mood, Th-1/Th-2 Cytokine Profile, and Autonomic Activity in Older Adults with Acute/Decompensated Heart Failure: Preliminary Observations*, 10 WORLD J OF BIOLOGICAL PSYCHIATRY 913 (2009) (Ex. 78)

[18] Dr. Larue is currently an Assistant Professor of Medicine at the Washington University School of Medicine. (Ex. B, p. 1.) He received his bachelor's degree from the University of Wisconsin and a Master of Population Health Sciences from Washington University School of Medicine. (*Id.*) Dr. Larue received his Doctor of Medicine from the Medical College of Wisconsin and although he does not have an active license to practice medicine in any state, he was previously licensed in Wisconsin and Missouri. (*Id*. at 1-2.) He is board certified in Advanced Heart Failure and Transplant Cardiology by the American Board of Internal Medicine. (*Id*. at 2.) Dr. Larue has authored 34 peer-reviewed articles and 4 book chapters. (*Id*. at 5-8.)

[19] Asked how his opinion would change if required to assume two areas of the heart were affected, Dr. LaRue indicated the change would be "slight." (Ex. E, p. 2.) Specifically, in that scenario he would opine that Takotsubo cardiomyopathy is the most likely diagnosis with his otherwise preferred explanation remaining the next most reasonable possibility. (*Id*.)

case for petitioner, he explains that the evidence is inconclusive. Dr. Lewis's report may be interpreted as implying that petitioner's LAD was at issue, but it is ambiguous. (Ex. E, p. 1.) Notably, a majority of Takotsubo patients have this anatomy. (*Id*. at 2.) Second, he stresses that petitioner's MRI ultimately only showed damage to the anterior wall. (Ex. A, p. 9.) He additionally explains that elevated white blood cell count, including elevated white blood cell count with a preponderance of neutrophils, is consistent with myocardial infarction itself. (*Id*. at 7-8.)

Dr. LaRue stresses that "[t]here is currently no scientific evidence of any relationship between influenza vaccine and myocardial infarction or ventricular arrhythmia. (*Id*. at 6.) He stresses that systematic review has shown the safety of the flu vaccine.[20] (*Id*.) Additionally, studies have specifically shown that the flu vaccine is associated with lower rates of cardiovascular morbidity and mortality.[21] (*Id*.) In particular, Dr. LaRue notes a study that compared the risk of myocardial infarction and stroke following influenza vaccination and systemic infection.[22] (*Id*. at 7.) The study found subjects had no increased risk of myocardial infarction for up to 91 days post-flu vaccination. (*Id.*) Dr. LaRue stresses that the Carty, Glaser, and Luibo studies cited by Dr. Stark have no evidence to indicate that the observation of elevated cytokines was clinically meaningful. (*Id*. at 8.) In contrast, he cites a study by Posthouwer, et al.,[23] which found that post-vaccination inflammation, measured by CRP, did not increase clotting ability. (*Id*.) Dr. LaRue notes that the Ritter case report involved an injury different than what this petitioner experienced. (*Id*. at 9.)

Asked by the special master for more information regarding elevated white blood cell counts among myocardial infarction patients, Dr. LaRue's third report provided citation to additional studies. (Ex. J, p. 1.) He asserts that a high proportion of myocardial infarction patients have elevated white blood cells. (*Id*.)

Dr. LaRue was also asked to respond to Dr. Stark's criticism that positive remodeling would occur gradually and would have been detectable by catheterization. He asserts that Dr. Stark "reverses the process." According to Dr. LaRue, positive remodeling is gradual, but it occurs prior to the myocardial infarction as plaque pushes the vessel outward. The acute myocardial infarction is the rupture. This dissolves the thrombus, leaving no significant lesion. (*Id*. at 2.) Dr. LaRue suggests that this process

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[20] Citing W.E.P. Beyer et al., Immunogenicity *and Safety of Inactivated Influenza Vaccines in Primes Populations: A Systematic Literature Review and Meta-Analysis*, 29 VACCINE 5785 (2011) (Ex. A, Tab 7).

[21] Citing Rohit S. Loomba et al., *Influenza Vaccination and Cardiovascular Morbidity and Mortality: Analysis of 292,383 Patients*, 17 J OF CARDIOVASCULAR PHARMACOLOGY AND THERAPEUTICS 277 (2012) (Ex. A, Tab 8).

[22] Citing Liam Smeeth et al., *Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination*, 351 NEW ENGLAND J OF MEDICINE 2611 (2004) (Ex. A, Tab 9). This article was additionally filed as Ex. 54 and Ex. C, Tab 5.

[23] D. Posthouwer, et al., *Influenza and Pneumococcal Vaccination as a Model to Assess C-Reactive Protein Response to Mild Inflammation*, 23 VACCINE 362 (2004) (Ex. A, Tab 11).

has been identified by two studies as occurring in approximately 40% of patients presenting with MINOCA. (*Id.* at 3-4.) He also posits that it may be possible that petitioner would have had detectable plaque if she had more sensitive intravascular ultrasound rather than coronary angiography. (*Id*. at 4.)

Like Dr. Morgan, Dr. LaRue provided a diagram illustrating the LAD and RCA. (*Id*. at 4-5.) Citing again to the study of Takotsubo patients raised in his prior report, Dr. LaRue opines that 83% of patients have the infero-apical wall supplied by the LAD. (*Id*.)

Asked whether he agrees that systemic inflammation can affect cardiac autonomic function, Dr. LaRue characterized the interplay as "complex." (*Id*. at 6.) He suggests that the studies cited by Dr. Stark would not support the suggestion that this would lead to myocardial infarction. (*Id*.)

Asked about the significance, if any, of the finding that petitioner did have atherosclerotic disease affecting her diagonal artery, unrelated to her myocardial infarction, Dr. LaRue contends that the fact that petitioner was a woman with any atherosclerotic disease at all means she was at statistically elevated risk for rupture of eccentric plaque with positive remodeling. (*Id.* at 7.)

Finally, Dr. LaRue indicates that following a review of literature, he finds no instance of Takotsubo syndrome from a systemic reaction. (*Id*.)

ii. Dr. Noel Rose, M.D., Ph.D. (immunology)[24]

Dr. Rose's written opinion stresses that epidemiology has not only failed to detect any association between the flu vaccine and heart disease, but studies have also found that vaccination can actually diminish the severity of heart disease and it is now common clinical practice to recommend the flu vaccine for cardiac patients at risk of enhanced disease.[25] (Ex. C, pp. 5, 9.) Dr. Rose stresses that the flu vaccine, in particular, does not utilize an adjuvant to boost the immune response to vaccination. (*Id*. at 4, 7.) According to Dr. Rose, petitioner's post-vaccination symptoms are attributable to a local inflammatory response rather than a systemic inflammatory response, with no systemic inflammation being evident. (*Id*. at 7.) Like Dr. LaRue, Dr. Rose does not find any of the studies cited by Dr. Stark (Carty, Fountoulaki, Glaser,

[24] Dr. Rose received his bachelor's degree from Yale and a master's degree and Doctor of Philosophy from the University of Pennsylvania. (Ex. D, p. 1.) He received his Doctor of Medicine from the State University of New York at Buffalo. (*Id.*) Dr. Rose authored over 800 publications, which include peer-reviewed articles and book chapters. (*Id.* at 7-44.)

[25] Citing Fountoulaki et al., *supra* n. 9, at Ex. 35; Andrzej Ciszewski et al., *Cardioprotective Effect of Influenza and Pneumococcal Vaccination in Patients with Cardiovascular Diseases*, 36 VACCINE 202 (2018) (Ex. C, Tab 3); Smeeth et al., *supra* n. 22, at Ex. A, Tab 9; and Michael M. McNeil et al., *Vaccination and Risk of Lone Atrial Fibrillation in The Active Component United States Military*, HUMAN VACCINES & IMMUNOTHERAPEUTICS 1 (Ex. C, Tab 19).

Liuba, Ritter) to be credible evidence of vaccine-causation, indicating that none of the studies show the observed inflammation to be affecting the heart. (*Id*. at 8-9.)

Dr. Rose was additionally asked to comment on petitioner's elevated temperature of 99.9°F upon emergency department presentation, along with her additional symptoms of headache, elevated white blood cell count and malaise, and whether that was indicative of a systemic inflammatory response. Dr. Rose responded that the "wisest course" in this case is to accept the evidence as suggesting "possible but low level" inflammation. (Ex. F, pp. 1-2.) Dr. Rose stresses that this petitioner's presentation is distinct from the type of "robust" and "body wide" cytokine response that leads to a multisystem reaction in what is known as a "cytokine storm." (*Id*. at 3.) Instead, Dr. Rose explains that low levels of systemic inflammation are well known in heart disease patients.[26] (*Id*. at 4.) He suggests that it is "hazardous to predict that a systemic inflammatory response will give a highly focused effect in particular coronary vessels." (*Id*.) In petitioner's case, he indicates that "low levels of circulating cytokines would be expected although they may not contribute to disease." (*Id*. at 5.) He opines that the absence of a cytokine storm leaves the suggestion of any exaggerated inflammatory response unsupported. (*Id*.) According to Dr. Rose, the fact that petitioner had only a "slight" increase in body temperature "demolishes" the proposal that petitioner suffered any exaggerated acute phase reaction to her flu vaccination. (*Id*. at 6.)

iii. Arnold Levinson, M.D. (immunology)[27]

Dr. Levison opines that "[w]hereas signs of inflammation such as local injection swelling and pain, low-grade fever, headache and myalgia, variously seen post-seasonal flu vaccine administration of healthy subjects, is consistent with the action of the observed post-inflammatory cytokines, there is absolutely no evidence that these levels of cytokines induce any kind of acute cardio-vascular inflammatory events in healthy subjects studied." (Ex. G, pp. 4-5.) He characterizes the idea that this petitioner represented a hypersensitive outlier as a "giant leap of faith." (*Id*. at 4.) He also opines that petitioner's elevated white blood cell count, including her preponderance of neutrophils, though potentially due to inflammation, are better explained by her treatment with glucocorticoid agents. (*Id*. at 6.) He stresses that this

[26] Citing Paul M. Ridker, *A Simple Test to Help Predict Risk of Heart Attack and Stroke*, 108 CIRCULATION e81 (2003) (Ex. F, Tab 2); Frederik Strang & Heribert Schunkert, *C-Reactive Protein and Coronary Heart Disease: All Said—Is Not It?*, 2014 Mediators of Inflammation 1 (2014) (Ex. F, Tab 3); Hafid Ait-Oufella et al., *Anticytokine Immune Therapy and Atherothrombotic Cardiovascular Risk*, 39 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 1510 (2019) (Ex. F, Tab 4); and Monika Bartekova et al., *Role of Cytokines and Inflammation in Heart Function During Health and Disease*, 23 HEART FAILURE REVIEWS 733 (2018) (Ex. F, Tab 5).

[27] Dr. Levinson is an Emeritus Professor of Medicine and Neurology at the University of Pennsylvania's Perelman School of Medicine. (Ex. H, p. 1-2.) He received his bachelor's degree and Doctor of Medicine from the University of Maryland. (*Id.* at 1.) Dr. Levinson is licensed to practice medicine in the state of Pennsylvania and is board certified by the American Board of Internal Medicine and the American Board of Allergy and Clinical Immunology. (*Id.* at 1.) He has authored 114 peer-reviewed articles and 45 peer-reviewed editorials, book chapters, and invited reviews. (*Id.* at 10-21.)

was recognized by petitioner's treating physician, Dr. Orlovic. (*Id.* (citing Ex. 8, p. 119).) Like Dr. Rose, Dr. Levinson disagrees with Dr. Stark's assessment that petitioner suffered any "exaggerated" immune response, noting that her symptoms are consistent with typical post-vaccination symptoms seen in large numbers of healthy vaccinees. (*Id*. at 5.)

Dr. Levinson notes, as did Dr. Rose, that epidemiology suggests that the flu vaccine has either a beneficial effect on cardiovascular disease or no effect at all.[28] (*Id*. at 5.) He also explains, as did Dr. LaRue, that the studies cited by Dr. Stark fail to show the observed inflammatory markers resulted in any severe adverse cardiovascular events. (*Id*. at 6-7.) Addressing Dr. Axelrod's discussion of vaccine-caused vasospasm, Dr. Levinson notes that most of Dr. Axelrod's discussion stems from studies relating to cerebrovascular vasospasm in the context of subarachnoid hemorrhage. (*Id.* at 5.) Dr. Levinson indicates that these studies mostly did not establish the cytokines as the principal inducers of the vasospasms and further did not exclude other by-products of the hemorrhagic event contributed.[29] (*Id*.) In any event, Dr. Levison considers it "questionable" to rely on the effects of subarachnoid hemorrhage as evidence relating to the effects of the flu vaccine on the coronary artery. (*Id*.) He acknowledges that the study by Li, et al., observed augmented inflammation among those with a history of variant angina, but explains the study did not evidence these markers as being related to vasospastic events. (*Id*.)

In response to questions by the special master, Dr. Levison indicated that a post-vaccination presentation inclusive of elevated temperature (99.9°F), injection site pain, malaise, headache, hives, and swelling, would constitute a systemic reaction; however, he stressed that it would be "mild," would not be expected to be a precursor to a myocardial infarction, and "is not tantamount to a pathologic or disease-causing process." (Ex. I, p. 1.) He again observed this type of presentation is often observed in healthy vaccinees. (*Id*.) Dr. Levinson was asked to opine whether a 31-hour onset period would be appropriate for a systemic inflammatory response leading to myocardial infarction, but indicated he cannot assess the appropriate temporal relationship because he remains unclear regarding what mechanism could cause such an event. (*Id*. at 2.)

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[28] Jacob A. Udell et al., *Association Between Influenza Vaccination and Cardiovascular Outcomes in High-Risk Patients: A Meta-Analysis*, 310 J OF THE AMERICAN MEDICAL ASSOCIATION 1711 (2013) (Ex. C, Tab 2); Jacob A. Udell et al., *Does Influenza Vaccination Influence Cardiovascular Complications?*, 13 EXPERT REVIEW OF CARDIOVASCULAR THERAPY 593 (2015) (Ex. C, Tab 1); Andrzej Ciszewski et al., *Influenza Vaccination in Secondary Prevention From Coronary Ischaemic Events In Coronary Artery Disease: FLUCAD Study*, 29 EUR HEART 1350 (2008) (Ex. 53); Fountoulaki et al., *supra* n. 9, at EX. 35; Smeeth et al., *supra* n. 22, at Ex. A, Tab 9; Orly Vardeny et al., *Influenza Vaccination in Patients with Chronic Heart Failure*, 4 J OF THE AMER COLLEGE OF CARDIOLOGY: HEART FAILURE 152 (2016) (Ex. C, Tab 6); C. Clar et al., *Influenza Vaccines for Preventing Cardiovascular Disease*, 5 COCHRANE DATABASE OF SYSTEMATIC REVIEWS 1 (2015) (Ex. C, Tab 11). The Vardeny et al. article was additionally filed as Ex. 55.

[29] Discussing Rasmussen et al., *supra* n. 10, at Ex. 36; Bowman et al., *supra* n. 11, at Ex. 45; Markus Lenski et al., *Interleukin 6 in the Cerebrospinal Fluid as a Biomarker for Onset of Vasospasm and Ventriculitis After Severe Subarachnoid Hemorrhage*, 201 WORLD NEUROSURGERY 132 (2016) (Ex. 42); and Fassbender et al., *supra* n. 11, at Ex. 43.

V. Discussion

a. *Althen* prong one

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549. Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon*, 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

There is no meaningful debate in this case that infection is associated with adverse cardiac events, probably including an inflammatory component. (Ex. C, p. 2.) There is also no significant debate that the flu vaccine produces temporary elevations in inflammatory cytokines. (Ex. G, p. 4[30] and Ex. 62, pp. 3-4[31]; *see also* Ex. C, pp. 6-7; Ex. I, p. 1; Ex. 29, p. 5; Ex. 73, p. 2.) Significantly, however, both parties' experts have come forward with literature demonstrating that the flu vaccine has a cardioprotective effect. (*See e.g.,* Fountoulaki et al., *supra* n. 9, at Ex. 35, p. 6; Ciszewski et al., *supra* n. 25, at Ex. C, Tab 3, pp. 2-4; Ait-Oufella et al., *supra* n. 26, at Ex. F, Tab 4, p. 4; Udell et al., *supra* n. 28, at Ex. C, Tab 1, p. 1; Ciszewski et al., *supra* n. 28, at Ex. 53, p. 1, 5.)

The reasons for this cardioprotective effect are not entirely clear, but may have to do simply with the ability of the flu vaccine to prevent infections, which are themselves associated with cardiovascular events. This likely leads to a statistical reduction in cardiovascular events. (*E.g.*, Udell et al., *supra* n. 28, at Ex. C, Tab 1, p. 1.) That does not in itself mean the flu vaccine is incapable of causing acute cardiac events such as myocardial infarction. However, it does mean that the inflammatory response to vaccination cannot be merely equated in its cardiovascular effects with infection. For example, Smeeth, et al., a study discussed by both parties' experts, examined 20,486 individuals that suffered myocardial infarction and 19,063 patients experiencing stroke to study whether the 90-day period following any inflammatory event (infection or vaccination) represented an elevated risk of cardiovascular adverse effect. The study detected the risk of myocardial infarction and stroke following infection, but found no

[30] Citing Christian et al., *supra* n. 13, at Ex. 38; Lisa M. Christian et al., *Proinflammatory Cytokine Responses Correspond with Subjective Side Effects After Influenza Virus Vaccination*, 26 VACCINE 3360 (2015) (Ex. G, Tab 2); Kawsar R. Talaat et al., *Rapid Changes in Serum Cytokines and Chemokines in Response to Inactivated Influenza Vaccination*, 12 INFLUENZA AND OTHER RESPIRATORY VIRUSES 202 (2018) (Ex. G, Tab 3); and Udell et al., *supra* n. 28, at Ex. C, Tab 2.

[31] Citing Fountoulaki et al., *supra* n. 9, at Ex. 35 and Kashiwagi et al., *supra* n. 12, at Ex. 39.

elevated risk following vaccination. (Smeeth, et al., *supra* n. 22, at Ex. A, Tab 9.) In a smaller prospective study of optimally treated coronary artery disease patients comparing 325 vaccinees against 333 patients administered a placebo, major adverse cardiac events (including myocardial infarction) occurred less often in the vaccinated group. (Ciszweski, et al., *supra* n. 28, at Ex. 53.)

Thus, without treating epidemiology as dispositive, petitioner's stressing of the various studies of record that merely demonstrate the flu vaccine to elevate cytokines to some degree, but without demonstration of any relevant adverse events, will not be persuasive without more. The Federal Circuit has previously stressed that a petitioner is not obligated to present an epidemiological case supporting her claim. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). Nonetheless, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018) (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.").

The four articles cited by Dr. Stark are inadequate to support his contention that the flu vaccine can cause myocardial infarction. Carty et al. examined inflammatory markers in 43 men with severe carotid artery disease and 61 men without. (Carty, et al., *supra* n. 6, at Ex. 67, p. 1.) They found "mild, but measurable" acute phase responses among both groups. Markers for CRP, IL-6, and serum amyloid-a (SSA) were higher in those with disease, but only significantly so for SSA. The authors did not report on adverse events and concluded only that acute phase response variability may be predictive of underlying vascular disease. Liuba et al. found that endothelial abnormalities in human vasculature can persist for up to two weeks following a flu vaccination; however, given the size of the study and limited follow up, the authors disclaimed any insight into the significance of this finding, noting instead that prior studies have shown the flu vaccine to be cardioprotective. (Liuba, et al., *supra*, n. 6, at Ex. 69, p. 8.) Glaser et al. found that patients with depressive symptoms may experience a stronger inflammatory response to vaccination with no indication the difference would affect cardiovascular health. (Glaser, et al., *supra* n. 6, at Ex. 68, p. 5.) Ritter et al. is a single case report[32] of a woman who experienced vasculitis and

[32] Generally, case reports offer circumstantial evidence of vaccine causation and therefore should not be summarily rejected. Case reports "'do not, [however,] purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'. . . [but] 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *Paluck ex rel. Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015)). Case reports often present a detailed report of symptoms, signs, diagnosis, treatment, and follow-up care. Oftentimes petitioners in the Program will highlight the usefulness of case reports in cases of novel, unusual or rare diseases. *See Patton v. Sec'y of Health & Human Servs.*, 157 Fed. Cl. 159, 166-67 (2021). *But see Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-39V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) ("single case reports of Disease X occurring after Factor Y . . . do not

myocardial infarction following a flu vaccine. (Ritter, et al., *supra* n. 6, at Ex. 71.) However, Dr. LaRue stresses that the subject's vasculitis distinguishes the case report from this case. (Ex. A, p. 9.)

Dr. Axelrod cites some of the same literature as Dr. Stark (most notably Liuba, et al., *supra* n. 6, at Ex. 69), but also more specifically seeks to bridge the remaining gap between vaccine cytokine response and cardiovascular injury by discussing vasospasms. Dr. LaRue agrees that coronary artery vasospasm is a potential cause of MINOCA. (Ex. A, p. 5.) However, the purported link to vaccination remains unpersuasive.

Dr. Axelrod relies in significant part on literature measuring cytokine levels relative to vasospasm in the context of subarachnoid hemorrhage, most notably a study by Rasmussen, et al. (Ex. 29, p. 3 (citing Rasmussen, et al., *supra* n. 10, at Ex. 36).) However, Dr. Levinson questions whether this is a relevant context for assessing coronary artery spasm. (Ex. G, p. 5.) Dr. Levinson's concern is especially well taken when comparing the Rasmussen study against the Fassbender study, a separate study cited by Dr. Axelrod regarding subarachnoid hemorrhage. (Fassbender, et al., *supra* n. 11, at Ex. 43.) The Fassbender study examined several cytokines, including IL-6 and TNF-α, using cerebral spinal fluid. (*Id*.at 1.) These cytokines were elevated among subarachnoid hemorrhage patients when measured this way and were correlated with cerebral vascular complications. (*Id.*) The authors explained that in the context of subarachnoid hemorrhage, the excessive inflammatory response originates in and is "compartmentalized" to the spine and subarachnoid space, specifically affecting the cerebral vasculature. (*Id*. at 1-3.) Moreover, although the manner by which cytokines contribute to cerebral vasospasms is not entirely clear, the current hypotheses include explanations that relate to specific features of the cerebral arteries. (*Id*. at 4.) In contrast, the Rasmussen study examined plasma cytokine levels as measured from peripheral blood samples. In pertinent part, that study found no association between vasospasms and either IL-6 or TNF-α. (Rasumussen, et al., *supra* n. 10, at Ex. 36, p. 5.) Thus, comparison between the Fassbender and Rasmussen studies suggests that what is true of cytokines within the central nervous system and cerebral vasculature is not necessarily true of cytokines circulating peripherally as measured from blood samples, leaving these studies far less persuasive with respect to what would affect the coronary arteries.

Dr. Axelrod stresses the Rasmussen study because it shows elevated cytokines associated with subarachnoid hemorrhage that are ultimately lower than what was observed post-vaccination in an unrelated study by Kashiwagi, et al. (Ex. 29, p. 3 (citing Kashiwagi, et al., *supra* n. 12, at Ex. 39).) Dr. Axelrod's comparison of the cytokine levels measured in Rasmussen to the post-vaccination cytokine levels observed in Kashiwagi is unpersuasive given that none of the cytokines measured in Kashiwagi were associated with vasospasm in the Rasmussen study. Dr. Axelrod's theory

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offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance"), ***aff'd***, 125 Fed. Cl. 251 (2014).

ultimately relates to vasospasm, not subarachnoid hemorrhage, and Dr. Axelrod has not substantiated that subarachnoid hemorrhage is of any relevance in itself. Nor did Kashiwagi, et al., examine cardiovascular events. Li, et al., does discuss elevated Il-6 and CRP as a marker among patients with variant angina. (Li, et al., *supra*, n. 11, at Ex. 44.) However, Dr. Levinson stresses that it does not evidence these markers as being causes of vasospastic events. (Ex. G, p. 5.) To the extent the authors hypothesize inflammation as a contributor to variant angina, they conclude it may be a chronic factor. (Li, et al., *supra* n. 11, at Ex. 44, p. 1.)

Dr. Axelrod additionally cites the Bowman study (*supra* n. 11, at Ex. 45), in which vasospasm of the femoral artery was induced by IL-6 *in rats* and the Gardiner study (*supra* n. 14, at Ex. 41), in which TNF-α and IL-1β were used to invoke cardiovascular response *in rats*; however, these studies are not persuasive given Dr. Axelrod's specific reliance on Rasmussen, et al. Regardless of what the rat models showed, Rasmussen found no association between either IL-6 or TNF-α and vasospasm *in humans*. (Rasumussen, et al., *supra* n. 10, at Ex. 36, p. 5.) Even setting the Rasmussen study aside, it is still not clear that these rat studies are reasonably similar to what petitioner's experts theorize happened in this case. Of note, the Bowman authors explain, consistent with the above, that their model is intended to mimic *cerebral* vasospasm and that human studies have reached inconsistent results with respect to whether cytokines contribute to subarachnoid hemorrhage. (Bowman, et al., *supra* n. 11, at Ex. 45, p. 4.)

Considering all of this collectively and in the context of the record as a whole, I conclude that petitioner has not preponderantly established that the flu vaccine can cause acute cardiac events, including myocardial infarction.

b. *Althen* prong two

The second *Althen* prong requires proof of a logical sequence of cause and effect demonstrating vaccine causation, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280) (stating that "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'"). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) (stating that "there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Ultimately, petitioner may support her claim either through his medical records or by expert opinion. § 300aa-13(a)(1).

Petitioner stresses in her brief that she did not have a history of heart disease or heart attack, quoting Dr. Stark's assessment that she was a woman "in excellent health, with a history of occasional migraine headaches" as well as Dr. Glickman's October 26, 2016, assessment of "no cardiac pulmonary GI or GU symptoms." (ECF No. 92, pp. 30-31 (quoting Ex. 25, p. 2; Ex. 3, p. 17).) Petitioner implies that, but for her proposed explanation of events, her condition would otherwise be mysterious or unlikely. Importantly, however, petitioner did have several risk factors for an acute cardiovascular event. Both Dr. Morgan for petitioner and Dr. LaRue for respondent agree that petitioner's atherosclerosis of the small diagonal artery (Ex. 5, p. 5) is significant to assessing her condition even though it is not directly implicated in her myocardial infarction. Specifically, they both opine that the fact of this finding makes it more likely that petitioner's myocardial infarction could have been caused by an undetected clot or plaque. (Ex. 80, p. 3; Ex. J, p. 7.) Additionally, petitioner also had a documented history of hypertension, which is a risk factor for atherosclerosis. (*Compare* Ex. 19, p. 3; Ex. 20, pp. 1, 6; Ex. 23, p. 4; Ex. 24, pp. 1,4 *with* Xue -Qiao Zhao, *Pathogenesis of Atherosclerosis*, UPTODATE (Ex. J, Tab 3, p. 8).) Further to this, petitioner's immunology expert, Dr. Axelrod, has filed review articles indicating that migraine disorders are considered an overall risk factor for cardiovascular disease. (Ex. 62, pp. 1-2 (citing Sacco, et al., *supra* n. 15, at Ex. 65, p. 3 and Saeed, et al., *supra* n. 15, at Ex. 66, p. 9).) While petitioner asserts this supports her claim because migraine disorders show a predisposition to vasospasm (ECF No. 96, pp. 3-4), the literature cited by Dr. Axelrod confirms the reason for the association between migraines and cardiovascular events is unknown. (Saeed, et al., *supra* n. 15, at Ex. 66, p. 3.) Thus, the evidence regarding migraines is sufficient only to establish that petitioner was statistically at risk for cardiovascular disease as a general matter, *i.e*., this was a risk factor regardless of what petitioner theorizes.

Petitioner also stresses the symptoms she experienced soon after vaccination, including swelling, hives, headache, arm pain, and malaise. (ECF No. 92, p. 31.) The fact of these symptoms is not reasonably contested. However, because Drs. Stark and Axelrod were not persuasive in establishing that post-vaccination inflammation is clinically meaningful to myocardial infarction, the fact that petitioner suffered constitutional symptoms following her vaccination is of diminished significance. Respondent's experts persuasively opined that, although technically systemic as petitioner contends, these symptoms are representative only of mild inflammation. (Ex. C, p. 7; Ex. F, p. 2.) As Dr. Levinson stressed, these symptoms commonly occur in healthy vaccinees and they are not established as a precursor to adverse cardiac events.

In addition to petitioner's post-vaccination symptoms, Dr. Stark cites two other factors as indicating petitioner's acute cardiac event was likely due to systemic inflammation. First, Dr. Stark stresses that multiple areas of the heart were affected. (Ex. 25, p. 3). He contends that this makes it far more likely petitioner's acute event resulted from a systemic cause. (*Id.*) There is a difference of clinical judgment between the parties' experts on whether Dr. Stark is correct to implicate two areas of damage.

(Ex. 25, p. 2; Ex. G, p. 3.) But regardless of whether petitioner's experts are more persuasive on that point, both Dr. LaRue and Dr. Morgan agree that while the two areas at issue may be supplied by two separate arteries, they can also be supplied by the same artery. (Ex. 80, p. 2; Ex. A, p. 7; J, pp. 4-5.) Although there is no definitive indication of which category petitioner falls into, this undercuts Dr. Stark's suggestion that damage to these two areas must *necessarily* be from a systemic source. Second, Dr. Stark stresses petitioner's WBC count as evidence petitioner was undergoing an inflammatory response. (Ex. 25, p. 3.) However, petitioner's immunology expert, Dr. Axelrod, and respondent's immunology expert, Dr. Levison, both opine that petitioner's WBC count was due to her treatment with glucocorticoid agents as observed by Dr. Orlovic. (Ex. 73, pp. 1-2; Ex. G, p. 6 (citing Ex. 8, p. 119).) Respondent's cardiology expert, Dr. LaRue, also suggests that elevated WBC would in any event be consistent with myocardial infarction itself. (Ex. J, p. 1.) Even to the extent Dr. Stark stresses the preponderance of neutrophils, Dr. LaRue explains that this too is consistent with myocardial infarction. (*Id.*)

Dr. Stark suggests that Dr. LaRue's alternative explanation reflects an unlikely series of events. (Ex. 58, p. 1.) However, Dr. LaRue indicates that Dr. Stark misinterpreted his opinion. (Ex. J, p. 2.) Specifically, Dr. Stark questioned why Dr. LaRue would opine that positive remodeling could happen within hours, but Dr. LaRue explained that his view is that the plaque buildup and positive remodeling occurred over time prior to vaccination. (*Id.*) Dr. Stark also questioned why, even if the plaque ultimately dissolved at the time of the acute event, there was not residual evidence of the plaque. (Ex. 58, p. 2.) Dr. LaRue offered a competing clinical judgment that this process can result in no remaining significant lesion. (Ex. J, p. 2.) He also suggests that some residual damage could be picked up by ultrasound rather than angiography. (*Id.* at 3.) Dr. Stark did not otherwise challenge Dr. LaRue's explanation of MINOCA more broadly, or his specific assertion that eccentric plaques are among the established causes of MINOCA. Petitioner's other cardiology expert, Dr. Morgan, likewise opines that it is possible for a blockage causing myocardial infarction to ultimately evade the cardiac catheterization imaging. (Ex. 80, p. 3.) As noted above, both Dr. LaRue and Dr. Morgan find significance in the fact that petitioner did have atherosclerosis of some degree, albeit in a location that was not implicated in her myocardial infarction. (*Id.*; Ex. J, p. 7.)

Finally, I have considered the views of petitioner's treating physicians, but do not find that any of the treating physician statements meaningfully support vaccine causation. Petitioner stresses that her physicians did not reach any alternative conclusion regarding the cause of her cardiac event and, in fact, opined that it was vaccine-caused. (ECF No. 92, pp. 33-34.) In particular, petitioner quotes the following by Dr. Miller, petitioner's treating cardiologist: "[i]it is very likely that her cardiac event in 2016 was Takotsubo syndrome, however her wall motion appears to have not recovered. The precipitating event is unclear, however appears to be related to the influenza vaccine." (*Id*. (quoting Ex. 27, p. 1).)

Dr. Miller's statement is not consistent with petitioner's claim given that it is premised on his acceptance that petitioner's history very likely constituted Takotsubo

syndrome. Her experts, by contrast, did not support such a view. Neither Dr. Stark nor Dr. Axelrod discussed Takotsubo syndrome as any part of their causal opinion. Dr. Morgan did indicate that Takotsubo syndrome can result from systemic inflammation, but this was not substantiated. (Ex. 80, p. 3.) Moreover, Dr. LaRue indicates that his review of the medical literature refutes that assertion. (Ex. J, p. 7.) In any event, Dr. Morgan opined that petitioner did not suffer Takotsubo syndrome. (Ex. 80, p. 3.) Without additional expert support, Dr. Miller's statement is inadequate standing alone to substantiate that the flu vaccine could reasonably be considered a precipitant of Takotsubo syndrome.

Moreover, considering the quotation from Dr. Miller as a whole, it is best interpreted as raising only a suspicion of vaccine causation. That is, prefaced with the caveat that the precipitating event is "unclear," use of the word "appears" falls short of stating a conclusion.[33] Indeed, petitioner acknowledges that "[t]his statement from a treating physician is basically indicating that we may never know for sure what happened to [petitioner]" but argues that it is an assertion that "based on the clinical presentation, the timing after immunization, and the lack of other precipitating events, it was probably the shot." (ECF No. 96, p. 6.) However, the Federal Circuit has explained that "[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant*, 956 F.2d at 1149). Thus, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *Isaac v. Sec'y of Health and Human Servs*., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012).

I have also considered the other treating physician statements contained in petitioner's medical records. In 2018, petitioner received a vaccine exemption from a physician's assistant in Dr. Lewis's office; however, the statement indicates only vaguely that her vaccine reaction "affected her heart." (Ex. 59, p. 2.) This is especially unpersuasive given the cardiologist's explicit conclusion that the precipitating event is unclear.[34] Other statements within the medical records document the fact of petitioner having experienced a post-vaccination reaction without linking that reaction to petitioner's cardiac condition. For example, her November 1, 2016, discharge includes "[status post] flu shot reaction" without any indication it was causally related to any of the other listed diagnoses. (Ex. 8, p. 18.) Dr. Orlovic and Dr. Mateo-Bilbeau both

[33] For example, a special master has previously explained that medical records may include notations where a physician "may well be indicating a *question* in the physician's mind whether there is a causal relationship, or a *suspicion* that there might be a causal relationship. However, that is quite different from an indication that such physician has reached a *conclusion* concerning a causal relationship." *Stapleford v. Sec'y of Health and Human Servs.,* No. 03-234V, 2009 WL 1456441, at *17 n.24 (Fed. Cl. Spec. Mstr. May 1, 2009) (emphasis in original), *aff'd*, 89 Fed. Cl. 456 (Fed. Cl. 2009). Here, Dr. Miller clearly states that, although the circumstances have the appearance of vaccine causation, the nature of the precipitating event is not known.

[34] Otherwise, "[a] treating physician's decision to administer or withhold a vaccination can be highly probative of causation." *Tarsell v. United States*, 133 Fed. Cl. 782, 797 (2017) (citing *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1376 (Fed. Cir. 2009))

recorded the history of vaccine reaction without assessing it as causally related. (Ex. 8, pp. 56-57; Ex. 6, pp. 26-30.) Several other records are limited to merely recording petitioner's own assertion that her cardiac event was due to her flu vaccination. (Ex. 20, p. 10; Ex. 61, p. 425; Ex. 60, p. 1.)

For all these reasons, I find that petitioner has not met her burden under *Althen* prong two of preponderantly establishing a logical sequence of cause and effect demonstrating that her flu vaccine did cause her injury.

c. *Althen* prong three

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

In this case, petitioner's experts opine that petitioner's cardiac event was caused by post-vaccination systemic inflammation. They assert that the event, occurring about 31 hours post-vaccination, happened during a timeframe in which it is medically reasonable to conclude that post-vaccination inflammation would be persisting. Rather than refuting this specific contention with respect to timing, respondent's experts primarily contest that the type of inflammation petitioner experienced could cause a cardiac event *at all*. Thus, for all the reasons discussed in the preceding sections, this case turns on *Althen* prongs one and two. Because *Althen* prong three coincides with *Althen* prong one, petitioner's inability to meet her burden under prong one effectively precludes her from being able to meet her burden under *Althen* prong three. Even assuming that petitioner satisfied *Althen* prong three, that alone would not satisfy petitioner's overall burden of proof. *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that a "temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury."); *Hibbard v. Sec'y of Health & Human Servs.*, 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding the special master did not err in resolving the case pursuant to Prong Two when respondent conceded that petitioner met Prong Three).

VI. Conclusion

There is no question that petitioner has suffered and that the events discussed throughout this decision profoundly affected her life. She has my sympathy and I do not question her sincerity in bringing this claim. However, for all the reasons discussed above, I find that petitioner has not met her burden of proof in this case. Therefore, this case is dismissed.[35]

IT IS SO ORDERED.

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

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