In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: December 2, 2025

DEBORAH MCNABB	*	
Petitioner,	*	No. 19-1185V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Meredith Daniels, Conway Homer, P.C., Boston, MA, for petitioner.
Nina Ren, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

On August 13, 2019, Deborah McNabb ("petitioner") filed her claim in the National Vaccine Injury Compensation Program.[2] Petition (ECF No. 1). Petitioner alleges that as a result of receiving the influenza ("flu") vaccine on September 29, 2016, she developed Drug Reaction with Eosinophilia and Systemic Symptoms ("DRESS") syndrome. *Id.* at Preamble; *see also* Petitioner's ("Pet'r") Brief ("Br.") at 1 (ECF No. 48). After a review of the record, I find that petitioner has established by preponderant evidence that she is entitled to compensation.

I. Procedural History

Petitioner filed her claim on August 13, 2019 and filed medical records to support her claim on September 4, 2019. Pet'r Exhibits ("Exs.") 1-22 (ECF Nos. 7—9). Respondent filed

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the decision will be available to anyone with access to the Internet.** Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

the Rule 4(c) Report on May 15, 2020 recommending against compensation, asserting that petitioner had yet to file sufficient evidence to support vaccine causation. Respondent ("Resp't") Report ("Rept.") (ECF No. 14).

Petitioner filed a response to respondent's Rule 4(c) report on June 15, 2020 and filed an expert report by immunologist, Dr. David Rosenstreich[3], and supporting medical literature. Pet'r Ex. 24, 26—41. Respondent filed an expert report from dermatologist, Dr. Emanual Maverakis[4], and medical literature, on April 27, 2021. Resp't Exs. A, Resp't Exs. A, Tabs 1-8 (ECF No. 26).

The undersigned held a Rule 5 Status Conference on October 1, 2021, after which I ordered petitioner to file a supplemental expert report. Rule 5 Order (ECF No. 29). Petitioner filed a supplemental expert report by Dr. Rosenstreich on December 2, 2021. Pet'r Ex. 42 (ECF No. 31). Respondent also filed a supplemental expert report by Dr. Maverakis on March 28, 2022. Resp't Ex. B (ECF No. 35). After unsuccessful litigative risk negotiations, petitioner filed a motion for a ruling on the record. Pet'r Br. (ECF No. 48). Respondent filed a response to petitioner's brief on April 4, 2024. Resp't Br. (ECF No. 52). Petitioner has not filed a reply. This matter is now ripe for adjudication.

II. Legal Standard for Adjudication

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

[3] Dr. David Rosentreich is currently the Director of the Division of Allergy and Immunology in the Department of Medicine at Albert Einstein College of Medicine and Montefiore Medical Center located in the Bronx, New York. Pet'r Ex. 25 at 1. He received his medical degree from the New York University School of Medicine in 1967, and is Board Certified in Allergy and Immunology, and is licensed to practice medicine in the State of New York. *Id.* at 2. He completed his residency at Bronx Municipal Hospital Center, then worked at the National Institute of Allergy and Infectious Disease section at the National Institutes of Health from 1969-1979. *Id.* at 1-2. In 1980, Dr. Rosenstreich began as an Associate Professor at Albert Einstein College of Medicine and also became an attending physician. *Id.* at 2. Dr. Rosenstreich has served as a member of the Data Safety Monitoring Board of the National Institute of Allergy and Infectious Disease for ten years, which was responsible for approving and supervising many types of human research studies, some involving vaccines. Pet'r Ex. 24 at 1. Additionally, Dr. Rosenstreich has published over 200 paper in the field of Allergy and Immunology, including articles that discuss multiple hypersensitivity disorders, including asthma, sinusitis, and urticaria. Pet'r Ex. 24 at 2; Pet'r Ex. 25. Dr. Rosenstreich is qualified as an expert in immunology and allergy.

[4] Dr. Emanual Maverakis is a professor of Dermatology at the University of California, Davis Medical Center in Sacarmento, California. Resp't Ex. A; Resp't Ex. D. Dr. Maverakis received his medical degree from Harvard Medical School in 2003 and completed his residency in dermatology at University of California, Davis in 2007. Resp't Ex. D at 5. From 2007-2013, Dr. Maverakis was a staff physician at the Northern California Health Care System of the Department of Veterans Affairs. *Id.* Dr. Maverakis became an Assistant Professor at the University of California, Davis Medical Center in the Department of Dermatology in 2007. He is Director of Immune Monitoring Shared Resource at the UC Davis Comprehensive Cancer Center at the University of California, Davis. Dr. Maverakis is board certified in dermatology and preventive medicine, and he is licensed to practice medicine in the State of California. *Id.* at 5. Dr. Maverakis has authored or co-authored 140 peer reviewed medical articles focusing on immune-mediated diseases. Resp't Ex. A at 1. Dr. Maverkais is qualified as an expert in dermatology.

a. Legal Standard for Fact Finding

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). A petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he or she] may find in favor of the party who has the burden to persuade the judge of the fact's existence. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010).

The process for making determinations in Vaccine Program cases regarding factual issues begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are generally considered to be more trustworthy. *Cucuras v. Sec'y of Health & Hum. Servs.,* 993 F.2d 1525, 1528 (Fed. Cir. 1993); *but see Kirby v. Sec'y of Health & Hum. Servs.,* 997 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying *Cucuras* does not stand for the proposition that medical records are presumptively accurate and complete). While not presumed to be complete and accurate, medical records made while seeking treatment are generally afforded more weight than statements made by petitioner after-the-fact. *See Gerami v. Sec'y of Health & Hum. Servs.,* No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013) (finding that contemporaneously documented medical evidence was more persuasive than the letter prepared for litigation purposes), *mot. for rev. denied,* 127 Fed. Cl. 299 (2014). Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006); *U.S. v. U.S. Gypsum Co.*, 333U.S. 364, 396 (1948).

The Vaccine Act requires petitioner to show by preponderant evidence that she "suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine." § 11(c)(1)(D)(i); *see Song v. Sec'y of Health & Hum. Servs.*, 31 Fed. Cl. 61, 65-66 (1994), *aff'd,* 41 F.3d 1520 (Fed. Cir. 2014). "The term 'residual effects…' requires a change within the patient that is caused by the vaccine injury." *Wright v. Sec'y of Health & Hum. Servs.*, 22 F.4th 999 (Fed. Cir. 2022). " 'Residual' suggests something remaining or left behind from a vaccine injury…Because vaccine injuries are somatic conditions defined by their signs and symptoms with the patient….their residues are similarly defined. *Id.* at 1005-06. The use of the words "suffered" and "complication" in association with "residual effects in § 11(c)(1)(D)(i) "suggests that Congress contemplated residual effects to be detrimental conditions within the patient, such as lingering or recurring signs and symptoms." *Id.* at 1006. Together, 'residual effects' and 'complications' appear to both refer to conditions within the patient, with 'residual effects' focused on lingering signs, symptoms, or sequelae characteristics of the course of the original vaccine injury, and 'complications' encompassing conditions that may not be 'essential part[s] of the disease' or may be outside the ordinary progression of the vaccine injury." *Id.*

b. Legal Standard for Causation

To receive compensation through the Program, petitioner must prove either (1) that [he] suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a

vaccine that she received, or (2) that he suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); *Capizzano v. Sec'y of Health & Hum. Servs.,* 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Because petitioner does not allege that he suffered a Table Injury, he must prove that a vaccine he received caused his injury. To do so, he must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and his injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("*Althen* Prong Three"). § 13(a)(1); *Althen*, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Recently, in *Kottenstette,* the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[.]" *Kottenstette v. Sec'y of Health & Hum. Servs.,* -- Fed.Appx.—(Fed. Cir. June 15, 2021) (citing *Knudsen v. Sec'y of Health & Hum. Servs.,* 35 F.3d 543, 549 (Fed. Cir. 1994). Causation "can be found in vaccine cases….without detailed medical and scientific exposition of the biological mechanisms." *Knudsen,* 35 F.3d 543, 548-49 (Fed. Cir. 1994). It is not necessary for a petitioner to point to conclusive evidence in the medical literature linking a vaccine to the petitioner's injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1325 (Fed. Cir. 2010).

Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in petitioner's favor when the evidence weighs in his favor. *See Moberly,* 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); *Althen*, 418 F.3d at 1280 (noting that "close calls" are resolved in petitioner's favor).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo,* 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, the *Daubert* analysis has been used in the weighing of the scientific evidence actually proffered and heard rather than as a tool for the pre-trial exclusion of expert testimony. *Davis v. Sec'y of Health & Hum. Servs*., 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in

Vaccine Program cases has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 742–45 (2009). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly,* 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Summary of Evidence Submitted

a. Medical Records

Prior to receiving the flu vaccine on September 29, 2016, petitioner was relatively healthy and a practicing registered nurse. Pet'r Ex. 18 at 1. On September 29, 2016, petitioner received the flu vaccine in her left deltoid. Pet'r Ex. 1 at 1.

On October 10, 2016, petitioner went to the Steward Hospital Emergency Facility in Quincy, MA, complaining of an "allergic reaction" that began 7 days prior as an itchy rash on her torso and neck while in South Carolina. Pet'r Ex. 8 at 6. Petitioner stated that the rash had spread to her back and woke up with an itchy red face with nasal congestion. *Id.* Additionally, petitioner reported that her throat felt funny and her voice was altered. *Id.* Benadryl provided no relief of symptoms. *Id.* The physical examination was positive for "diffuse maculopapular rash all over the torso and back and minimally on the forearms and legs." *Id.* at 8. Swelling was noted on her face with erythema and papularity. *Id.* Petitioner was prescribed prednisone and hydroxyzine and referred to dermatology. *Id.*

The same day, October 10, 2016, petitioner presented to dermatologist, Dr. Kenneth Reed, for a rash located on her neck and trunk. Pet'r Ex. 9 at 6. Petitioner described the rash as itchy, painful, and red, and present for one week. *Id.* At this appointment, petitioner told Dr. Reed that the rash began right after she got the flu shot, but that she is not allergic to eggs. *Id.* Dr. Reed agreed with the recommended treatment plan provided from the emergency room and diagnosed petitioner with a hypersensitivity reaction with erythematous papular eruption distributed on the trunk. *Id.* Dr. Reed also noted that petitioner had the flu vaccine, and this was a "possible reaction to it." *Id.* He explained, "Hypersensitivity reactions may result from a medication, a viral illness, or even from an insect bite. Often it is difficult to determine the cause, but in this instance, she developed a measles like eruption about 1 week after her MMR vaccine, which is typical time onset for a vaccine related eruption." *Id.* Dr. Reed instructed the petitioner to return if her condition does not improve or if she develops additional symptoms. *Id.*

Three days later, on October 13, 2016, petitioner went to urgent care for "a rash starting 10 days ago," and "four days after flu vaccine." Pet'r Ex. 15 at 31. The "History of Present Illness" noted that petitioner was on a prednisone taper that started at 60 mg twice a day that had improvement of her facial rash, but not the rash on her body. *Id.* Petitioner was given Permethrin, an external skin cream to use all over her body and a referral to a dermatologist. *Id.* Petitioner went back to Derm ASAP on October 18, 2016 for a follow-up and was seen by nurse practitioner ("NP") Cohen. Pet'r Ex. 9 at 1-3. Petitioner reported that the Permethrin had not relieved her rash symptoms, and that the rash continued to be burning and itchy. *Id.* The physical examination showed that the rash was present almost all over her body and she was diagnosed with dermatitis that was inadequately controlled. *Id.* at 2. The differential diagnosis included "hypersensitivity reaction," and petitioner was instructed to discontinue all unnecessary medications and give a prescription of a topical steroid lotion. *Id.* at 4. A biopsy of her left forearm was taken. *Id.*

The biopsy result was negative for a fungal infection but was "consistent with a hypersensitivity reaction such as arthropod assault," as the skin biopsy showed "multifocal parakeratosis with inflamed scale crust and underlying superficial perivascular lymphocytic infiltrate. Pet'r Ex. 9 at 9.

On October 21, 2016, petitioner sought treatment with allergist, Dr. Karen Hsu Blatman at Brigham and Women's Hospital for the rash and itching that was all over her body. Pet'r Ex. 4 at 55. This appointment provides a more detailed timeline of events, and states:

> [Petitioner] states that she was in South Carolina from September 22-26…[on] September 29 she believes she may have had her influenza vaccine; on October 7th, which was Friday, two weeks ago, she started having sinus congestion, chest rash, and then she developed some hives on her face. On Saturday and Sunday, she was having trouble with a lot of sneezing, which then spontaneously resolved. But, the rash started to worsen. On Monday, October 10th, she felt like her voice had changed and hat she was having some trouble with respiratory symptoms and she describes having hives all over her face with some swelling and she had new diffuse bumpy rash over her upper back. She was seen in the ED in Quincy that day and was given prednisone starting at 40 mg a day, tapering for 10 days. Her last dose was three days ago, on 10/18. She was also given hydroxyzine pruritus, but she did not feel like it was really touching the pruritus.
>
> She was then sent to Dr. Reed, a dermatologist in Quincy. She felt like each dot felt like there are 10 hornets trying to get out of her skin and she feels a completely and extreme constant itch. On Thursday, Oct. 13th she was seen in urgent care in Weymouth and that doctor thought it might be atypical scabies and was to use permethrin…she had relief for about 15 minutes and then it started getting itchy….She once followed-up with Dr. Reed, the dermatologist earlier this week…and had a skin biopsy done by one his nurse practitioner, she also started using clobetasol mix and has been taking Allegra daily.

Id. at 57—8. Multiple excoriations throughout her arms and legs with ecchymoses on her right thigh were observed. *Id.* at 58. Petitioner had minimal papules on her back. *Id.* Dr. Blatman

ordered a complete blood count and checking serologies of IgG and total IgE. *Id.* at 59. Petitioner was referred to dermatologist, Dr. Yang, the same day.

Petitioner had her appointment with dermatologist, Dr. Yang later on October 21, 2016, where he mostly repeated petitioner's HPI from her appointment with Dr. Blatman, but he also noted, "Pt got flu shot in late September. On 10/7 had sinus congestion and chest rash. It later spread to her face. On the 10th, pt had trouble breathing and the rash had spread diffusely on her back, her face was also swollen….Pt saw a dermatologist, who gave clobetasol solution and did biopsy. Pt states the solution is not helpful at all." Pet'r Ex. 4 at 95. Dr. Yang observed faint erythematous macules and papules on petitioner's chest and back, and faint papular rash with ill-defined erythematous in the background on her arms, along with scattered excoriated papules on arms, abdomen, and legs. *Id.* at 98. Dr. Yang diagnosed petitioner with "rash, likely hypersensitivity reaction to component of flu vaccine," and noted that petitioner's CBC was remarkable for elevated eosinophils and ALT. *Id.* Petitioner was given a course of prednisone 60 mg to take daily and return in one week. *Id.* Dr. Yang also ordered labs to check petitioner's HHV-6 PCP.

Petitioner's EBV IgG was negative and her HHV-6 had a positive result. Pet'r Ex. 2 at 70. On October 25, 2016, petitioner called Dr. Yang's dermatology office because she was "very anxious and concerned regarding her test results which were released via patient gateway." Pet'r Ex. 4 at 146. Dr. Emily Baumin spoke to petitioner on the phone and stated, "there [was] some initial concern for a severe drug reaction given her initial laboratory testing and that she was empirically treated with steroids. I explained that the HHV6 test is a virus whose reactivation is associated with drug reaction eosinophilia systemic syndrome ("DRESS")." *Id.* at 145-46.

Petitioner returned to Dr. Yang on October 28, 2016 for a follow-up of her "generalized rash thought likely DRESS from flu shot." Pet'r Ex. 4 at 150. Dr. Yang recounted that petitioner's labs were "remarkable for eosinophilia, HHV-6 of 2300 and ALT of 133," and that an EKG showed some nonspecific abnormalities. *Id.* Petitioner reported significant improvement with the course of prednisone and TAC ointment. *Id.* No new lesions appeared but her existing ones were still somewhat pruritic. *Id.* Dr. Yang diagnosed petitioner with "generalized rash, thought likely DRESS from flu shot," and he stated that petitioner's "initial labs remarkable for eosinophilia, HHV-6 of 2300, and ALT of 133. Repeat labs done at South Shore show that ALT has come down to 53 and eosinophilia is resolved. *Id.* at 152—53. Petitioner was directed to continue the 60 mg of prednisone for another week and begin a steroid taper and continue to use of the TAC ointment. *Id.* at 153.

Petitioner had an appointment with Dr. Nikita Fitzcharles on October 31, 2016 for a medication review and follow-up. Pet'r Ex. 2 at 129. Petitioner reported that she had been diagnosed with "DRESS related supposedly to receiving the most recent influenza vaccine at her place of employment in…September." *Id.* at 131. She is taking a high dose of oral prednisone as part of her treatment and had a follow-up with her dermatologist for DRESS. *Id.* Petitioner expressed concern about how the prednisone could affect her bone density and was told in the past that she had osteopenia, and she was also worried about her triglyceride levels found in her latest bloodwork. *Id.* A bone density scan was ordered to address petitioner's concerns about

osteopenia and petitioner was given a free glucometer as she was now in the diabetic range with her A1C level at 7.6%. *Id.* at 132. Petitioner was also given a prescription of fenofibrate to address her hyperlipidemia. *Id.*

Petitioner had a follow-up appointment on November 3, 2016 with dermatologist Dr. Reed. Pet'r Ex. 9 at 9. At this appointment, petitioner reported that Dr. Yang had diagnosed her with DRESS "probably related to the vaccination (flu) she had earlier," and she was taking prednisone. *Id.* Petitioner also stated that when she initially sought treatment with Dr. Reed, her lesions were more localized, but by the time she went to Bringham the lesions were more generalized and the itching was worse. *Id.* Petitioner was diagnosed with a hypersensitivity reaction. *Id.* at 9.

Petitioner returned to Dr. Yang on November 8, 2016 for a follow-up of her DRESS diagnosis. Pet'r Ex. 4 at 169. He wrote that her "DRESS…most likely triggered from influenza vaccine that patient received on 9/29/2016." *Id.* Dr. Yang stated that "the only other drugs at that time was HCTZ and Synthroid, which patient had been taking for 20 years, and Lipitor, which patient has been taking for 1.5 years; *it is extremely unlikely for these to be the culprit as DRESS usually occurs 1-8 weeks after trigger." Id.* (emphasis added). Petitioner's rash had resolved and her labs were returning to baseline. *Id.* Petitioner had begun the prednisone taper. *Id.* Petitioner's diagnosis remained, "DRESS, most likely from flu shot," and directed petitioner to "avoid flu vaccine in future." *Id.* at 172. Dr. Yang continued petitioner on the prednisone taper and told her to follow-up in three weeks. *Id.*

Petitioner had an appointment with Dr. Rajesh Garg, an endocrinologist, for her elevated A1C levels. Pet'r Ex. 4 at 196. Petitioner thought that her elevated sugar levels was related to the prednisone she was taking. *Id.* Dr. Garg noted that petitioner was "extremely anxious and worried due to diabetes." *Id.* at 200. He increased her Metformin to 1000 mg as needed and instructed her to test her blood glucose level once daily at different times. *Id.* Additionally, he ordered a C-peptide and Anti-GAD antibody tests. *Id.*

Petitioner had a follow-up appointment with dermatologist, Dr. Yang, on January 26, 2017. Pet'r Ex. 4 at 303. Petitioner had completed her prednisone taper successfully in December and her repeat echocardiogram was normal. *Id.* However, about a week before this appointment, petitioner woke up with itchy arms and legs, used the cream she had previously been prescribed and the itching resolved. *Id.* The itching lasted two days but then resolved. Petitioner was still concerned about her symptoms and got a repeat CBC, CMP, and EKG. *Id.* Dr. Yang performed a skin inspection and noted that she had xerosis, but no skin lesions or facial swelling. *Id.* at 305. He assessed her with "DRESS-most likely from flu shot, resolved. Repeat labs remarkable for mild elevation of ALT and EKG abnormalities." *Id.* Dr. Yang wrote, "Informed patient that I am not concerned about recurrence of DRESS at this time. Elevated ALT most likely 2/2 fenofibrate, which patient was recently started [on] for hypertension. Patient to discuss with primary care physician about fenofibrate." *Id.* He also told petitioner that her cardiologist should review her EKG with her and determine if a further work-up is necessary. *Id.* Additionally, Dr. Yang diagnosed petitioner with pruritus 2/2 xerosis and recommended she avoid hot water and use mild soaps, and apply moisturizers while her skin was still wet. *Id.* at 306.

On January 30, 2017, petitioner had an MRI of her right foot for evaluation of possible stress fracture. Pet'r Ex. 15 at 51. The MRI found "mildly increased signal within the bone marrow of the fifth metatarsal shaft likely the sequela of a stress related injury. No evidence for a displaced fracture." *Id.*

Petitioner had an appointment with Dr. Nikita Fitzcharles on February 3, 2017 for a follow-up for "multiple concerns." Pet'r Ex. 2 at 125, 127. Petitioner had a possible hairline fracture of the 5th metatarsal after having a fall, injuring her right foot, which petitioner associated with osteopenia and risk associated with her prolonged use of oral steroids for treatment of her DRESS. *Id.* at 127. Although at this appointment, petitioner was no longer taking steroids. Petitioner also explained that recent bloodwork showed a TSH level of 0.26 and petitioner self-discontinued use of levothyroxine 88 mg because she was afraid from suffering a repeat/recurrent DRESS syndrome. *Id.* D. Fitzcharles counseled petitioner about risks related to osteopenia and developing osteoporosis and did not recommend that petitioner begin bisphosphonate, and petitioner insisted on being referred to an endocrinologist. *Id.* at 128. Dr. Fitzcharles also assessed petitioner with hypothyroidism and stated, "patient with history of Graves Disease as a result of radiation therapy and subsequent development of hypothyroidism." *Id.*

Nearly five months later, on June 9, 2017, petitioner had an appointment with Dr. Fitzcharles to review her labs. Pet'r Ex. 15 at 56. Dr. Fitzcharles explained that the most recent labs only showed a past infection of HHV-6. *Id.* Petitioner also reported she has only had one 48-hour episodes in which she had itching since her DRESS diagnosis last October. *Id.* Petitioner's ankle stress fracture had healed, and petitioner reported some weight loss. *Id.* Petitioner was diagnosed with Type 2 diabetes mellitus without complication and hypothyroidism. Additionally, Dr. Fitzcharles assessed petitioner with "DRESS," but wrote:

> Symptoms of DRESS last fall, was told at that time she may have sustained damage to the heart from the stress of the condition, referring for cardiac evaluation following management and treatment, and possibly an echocardiogram to evaluate for any lingering damage.

Id.

Prior to her appointment with Dr. Fitzcharles, petitioner had undergone additional blood work. The lab test results showed petitioner had high HHV-6 antibodies, indicative of a "past infection," and the interpretation on the lab results stated:

> In seroepidemilogy studies of the prevalence of exposure using serum screening dilutions of 1:10, the detection of IgG antibody in a mid-life population approaches 100%. Due to this high prevalence of HHV-6 antibody, correlation of single IgG titers with specific diseases are of little clinical value. Evidence of acute infection or reactivation of HHV-6 is demonstrated by a significant rise or seroconversion of IgG and IgM titers.

Id.

On August 15, 2017, petitioner had an appointment with Dr. Isabelle Zamfirescu, an endocrinologist, for an evaluation for type 2 diabetes and hypothyroidism. Pet'r Ex. 15 at 62. Petitioner reported that in February 2016, she had acute pancreatitis and then in October 2016, she developed DRESS following an adverse reaction to the flu vaccine. *Id.* Petitioner stated that she was on "high dose prednisone for DRESS and Hba1c of 7.6 in 10/2016." *Id.* Petitioner also noted that she has a history of hypothyroidism and was feeling well with Synthroid 88 mg six days a week. *Id.* Dr. Zamfirescu diagnosed petitioner with Type 2 diabetes that was well controlled and petitioner was advised to cut back on testing and mild hypertriglyceridemia and recommended a low dose of Atorvastatin. *Id.* at 64.

Petitioner went to cardiologist, Dr. Pranitha Reddy on August 31, 2017 for a cardiac screening. Pet'r Ex. 12 at 1. At this appointment, petitioner reported that she had "a history of DRESS diagnosed last fall reportedly secondary to influenza vaccine. She has been referred for evaluation of cardiac involvement. She states that her rash almost completely resolved and she no longer is on steroids." *Id.* Petitioner also stated that her recent echocardiogram revealed a structurally normal heart. *Id.* Petitioner denied a prior cardiac disease, chest pains, or palpitations. *Id.* Petitioner associated the onset of her diabetes with being on steroids. *Id.* Dr. Reddy performed a cardiovascular screening, diagnosed petitioner with cardiovascular risk factor and hypertension and wrote:

> 1. Cardiovascular screening: DRESS syndrome has been associated with cardiac involvement, including eosinophilic myocarditis though [petitioner] was reportedly without cardiac symptoms during her acute phase last fall. EKGs done at the time are not available though current echocardiogram and EKG are unremarkable. Literature review illustrates that patients can present with fulminant myocarditis events months after initial treatment.

Id. at 4.

Approximately 16 months later, on May 2, 2019, petitioner went to South Shore Allergy and Asthma for an evaluation for "food allergy." Pet'r Ex. 23 at 2. Petitioner reported that three days ago she ate steam clams and approximately 90 minutes after eating the clams she noted some facial flushing, and then thirty minutes after the onset of flushing, she developed loose stools. *Id.* About four hours after eating the clams, petitioner developed itching on her arms and chest and then developed hives and an erythematous bumpy rash on her thighs. *Id.* Petitioner's gastrointestinal issues resolved the next day, but she had a generalized rash. *Id.* She took Benadryl at work, and by the afternoon, she had developed chills. *Id.* Petitioner took Benadryl again before bed, but woke up overnight with wheezing and difficulty breathing, which resolved after taking an albuterol. *Id.* Petitioner reported never having a shellfish allergy and had never had issues with clams specifically. *Id.* At this appointment, petitioner also explained her allergic reaction to the flu vaccine in October 2016, and how she was on prednisone for two months and reported that "it took over 6 months for her eosinophil count and HPPV-6 level to normalize." *Id.* Dr. Young assessed petitioner for a shellfish allergy, acute urticaria, mild intermittent asthma, drug allergy, and drug-related rash and wrote:

> Her constellation of symptoms, especially chills, rhinitis, wheezing, loose stools, suggest viral syndrome; presentation for food allergy atypical in terms of symptom onset and persistence of symptoms.

Id. at 5. Dr. Young noted that petitioner had her primary care physician order labs and asked her to return the following Tuesday for a skin allergy test to clams. *Id.*

Over two years and seven months later, on May 6, 2019, petitioner called Brigham and Women's Hospital Dermatology Department and reported having a rash and itch all over her body. Pet'r Ex. 22 at 62. The record states that petitioner "had clams at home on Monday after that she started having rashes, then loose stools. No prior allergies to clams or sea food. She feels the rash looked similar to the DRESS syndrome rash. Reports intermittent chills and fever like when she had DRESS, she feels stress might have reactivated it." *Id.*

Petitioner had an appointment with Dr. Yang on May 7, 2019, when she repeated her symptoms after eating clams, similar to the explanation given to Dr. Young. Pet'r Ex. 22 at 26. However, she also explained that her labs from primary care physician demonstrated high eosinophils, mildly elevated CRP and increased HHV-6 titers, but her kidney and liver numbers were normal. *Id.* Petitioner stated that she was taking Cetirizine 10 mg for the rash and the rash has mostly resolved. *Id.* Petitioner inquired as to whether if her DRESS was recurring. *Id.* After an examination and a review of her labs, Dr. Yang assessed petitioner with "Rash, favor hypersensitivity reaction based on history, resolving on its own. *I do not suspect DRESS at this time*." *Id.* at 28 (emphasis added). He continued, stating:

> Suspect hypersensitivity reaction, given distribution and timing. Discussed pathophysiology and timing with patient. No causative agent identified, but patient will be alert to possible causes should the rash recur in the future. Patient's bloodwork was reviewed in detail and I explained to her that high eosinophil and elevated CRP can be seen with any hypersensitivity reaction.
>
> Ordered ECG (as patient had ECG abnormalities during her previous episode of DRESS, which I do NOT favor at this time, but patient would like repeat ECG to feel assured).

Id.

Dr. Yang called petitioner on May 10, 2019 after reviewing lab results and informed her that her labs were "remarkable for elevated HHV-6 and eosinophils," and he opined that petitioner's rash was likely due to a reactivation of HHV-6. *Id.* at 34; *see also* Pet'r Ex. 22 at 41 (lab results documenting elevated HHV-6 titers). He did not recommend any additional treatment, given the lack of systemic involvement and quick improvement in the rash. *Id.*

b. Petitioner's Expert's Reports—Dr. David Rosenstreich

Petitioner submitted two expert reports from Dr. David Rosenstreich. Pet'r Ex. 24 & 42. Dr. Rosenstreich reviewed petitioner's medical history through her records and stated that she had a history of "chronic asthma, intermittent sinusitis, hypertension and hypothyroidism

(following Grave's disease and treatment with radioactive iodine in 1994)" and "chronic osteopenia and had developed a third metatarsal stress fracture at one point." Pet'r Ex. 24 at 4. He also noted that petitioner had an electrocardiogram on February 14, 2016, approximately, 7 months prior to receiving the flu vaccine at issue, which had "nonspecific ST abnormalities," and that she also previously had abnormal liver function tests in February 2016 that resolved. *Id.*

Dr. Rosenstreich opined that petitioner developed Drug Reaction with Eosinophilia and Systemic Symptoms syndrome approximately four to seven days after she received the Fluarix vaccine on September 29, 2016. *Id.* He opined that petitioner "experienced a severe allergic reaction to the influenza vaccine" and her initial symptoms included "a generalized pruritic and painful rash, bruising, leg swelling, nasal congestion, and hoarseness." *Id.* at 8. Dr. Rosenstreich stated, "Because of associated laboratory abnormalities (eosinophilia, abnormal liver function tests, ECG abnormalities and elevated blood levels of HHV-6 viral DNA) suggesting a more severe, systemic inflammatory reaction, she was diagnosed by several medical specialists as having DRESS." *Id.*

Dr. Rosenstreich also stated that petitioner was initially treated with high-dose steroids and the rash finally resolved in approximately 6 weeks, but that petitioner experienced "periodic (every few week) relapses of rash lasting 48- hours," and that "some of these episodes included painful rash, chills and muscle aches, and these recurrences lasted at least until June 2017, 9 months after the initial vaccination. *Id.* Dr. Rosenstreich also associated petitioner's "worsening diabetes" as a result of her prolonged use of prednisone. *Id.* He noted that petitioner had an event in May 2019 that he called a "possible DRESS relapse" which was "possibly related to ingesting clams," when she developed generalized urticaria, chills and fever, associated with eosinophilia, and signs of systemic inflammation. *Id.* While he did not fully endorse petitioner's progressive leg pain and neuropathy in her left arm as to be wholly related to DRESS, Dr. Rosenstreich stated that petitioner's primary care physician was considering the neuropathy to possibly related to DRES in June 2019.

In his first report, Dr. Rosenstreich described DRESS as a "drug-induced hypersensitivity reaction whose manifestations include a skin rash, eosinophilia and involvement of other internal organs such as the liver." *Id.* at 9. The 2006 and 2019 Shiohara articles explain that DRESS typically starts 2—3 weeks after the induction of a drug and that the "delayed onset in relation to the introduction of the causative drug is one important feature of DRESS that can be distinguished from other types of drug eruptions." Pet'r Ex. 36 at 2[5]; Pet'r Ex. 29[6] at 2. DRESS typically begins with a fever shortly followed by a maculopapular rash, which may be purpuric and symmetrically distributed on the trunk and extremities. Pet'r Ex. 29 at 3; Pet'r Ex. 36 at 4. Both articles explain that the early phase of the cutaneous lesions are periorbital and facial edema with pinhead-sized pustules. Pet'r Ex. 29 at 3; Pet'r Ex. 36 at 4. Cervical lymphadenopathy is present in most patients early in the illness. Pet'r Ex. 36 at 4. Transient

[5] Shiohara, T. et al., *Drug Induced Hypersensitivity Syndrome (DIHS): A Reaction Induced by a Complex Interplay among Herpesviruses and Antiviral and Antidrug Immune Responses,* 55 Allerol. Internat. 1-8 (2006). [Pet'r Ex. 36].

[6] Shiohara, T. & Mizukawa, Y., *Drug-induced Hypersensitivity Syndrome (DiHS)/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Update in 2019*, 68 Allerg. Int. 301-308 (2019). [Pet'r Ex. 29].

eosinophilia is often present, and may be delayed 1—2 weeks, even after elevations of liver enzymes return to baseline. Pet'r Ex. 29 at 4. Elevation in liver enzymes occurs in approximately 70% of DRESS patients at the acute phase and "a marked decrease in serum IgG is typically observed in the acute phase," and "at its nadir, around 1—2 weeks after onset, the Ig levels may fall as low as 300-600 mg/dL." *Id.* at 4. Further, HHV-6 reactivation, "as evidenced by the significant increase in serum IgG titers to HHV-6 and the detection of HHV-6 DNA in leukocytes can be observed in the vast majority of DRESS patients at a certain time point, 2—3 weeks after onset." *Id.*

The diagnostic criteria for DRESS as set forth by RegiSCAR and the Japanese Consensus Group ("JCG") are the following:

DRESS Diagnostic Criteria by RegiSCAR	**DRESS Diagnostic Criteria by JCG**
Acute Rash	Maculopapular rash developing >3 weeks after starting with a limited number of drugs
Reaction suspected drug-related	Prolonged Clinic Symptoms after Discontinuation of Drug
Hospitalization	Fever
Fever (>38 degrees C)	Liver abnormalities (ALT >100U/L)
Laboratory Abnormalities with at least one present: lymphocyte above/below normal; low platelet; eosinophilia	Leukocyte abnormalities (at least one present): leukocytosis; abnormal lymphocytosis; eosinophilia (>1.5 x 10/L)
Involvement of one more internal organ	Lymphadenopathy
Enlarged lymph nodes at two or more sites	HHV-6 Reactivation

Pet'r Ex. 29 at 3. Important to this case, for a diagnosis of DRESS using the RegiSCAR criterion, "the first three criteria are necessary for diagnosis, and the presence of 3 out of the other 4." *Id.* Typical treatment of DRESS is with systemic corticosteroids for approximately 6-8 weeks and then ongoing monitoring to prevent the relapse of symptoms. Pet'r Ex. 36 at 6.

Regarding petitioner's diagnosis, Dr. Rosenstreich stated that at least three of petitioner's treating physicians diagnosed her with DRESS. Pet'r Ex. 24 at 10. He stated that petitioner's symptoms were consistent with DRESS, including the eosinophilia finding of greater than 700 K/uL, a rash covering more than 50% of her body, initial facial swelling and purpura, and liver involvement. *Id.* He stated that the "finding of increased blood levels of HHV-6 DNA makes the diagnosis of DRESS even more likely." *Id.* Dr. Rosenstreich wrote, "This constellation of findings is strong evidence that [petitioner] had experienced a powerful, systemic, immunologic/inflammatory reaction caused by the influenza vaccination that if it was not exactly typical DRESS, was at least-DRESS like in its manifestations and consequences." *Id.* Dr. Rosenstreich also stated that he could not be certain that the transient ECG abnormalities that petitioner developed were DRESS-related, as she had experienced a similar event prior to the flu vaccination, and two of petitioner's treating cardiologists did not feel that they were significant. *Id.*

Dr. Rosenstreich's supplemental report addressed Dr. Maverakis' opinion that petitioner would not meet the criteria for DRESS. Pet'r Ex. 42. While Dr. Maverakis took issue with the fact that petitioner did not have a fever or enlarge lymph nodes, Dr. Rosenstreich observed that lymphadenopathy is not present in 35-46% of patients in DRESS, and that while petitioner did not have a fever, she did present with hoarseness and congestion, consistent with DRESS. Pet'r Ex. 42 at 3, citing Pet'r Ex. 43 at 5[7]; *see also* Pet'r Ex. 29 at 3 ("they may be an upper-airway infection-like prodrome"). Additionally, Dr. Rosenstreich referred to petitioner's labs taken on October 21, 2016, which showed an elevation of eosinophils of 760 K/ul, contradicting Dr. Maverakis' opinion that petitioner did not have elevated eosinophils during the initial phase. Pet'r Ex. 42 at 5; *see also* Pet'r Ex. 4 at 67. With respect to the HHV-6 finding in petitioner's records, Dr. Rosenstreich stated that this was not a "nonspecific finding," but actually very relevant to the diagnosis of DRESS, as reactivation of viruses from the Herpesviridae family, including HHV-6, "is a known phenomenon associated with DRESS and occurs in up to 75% of patients." Pet'r Ex. 42 at 4. Dr. Rosenstreich's statement is supported by the articles by Shiohara, Lee, and Tohyama, which all explained that HHV-6 reactivation is present in a majority of probable/definite DRESS patients. *See* Pet'r Ex. 29 at 2; Pet'r Ex. 43 at 7; Pet'r Ex. 47 at 1.[8]

DRESS is thought to be a T-cell mediated disease and the symptoms associated with DRESS are "associated with an oligoclonal proliferation of activated CD8-T lymphocytes that are directed against viral antigens derived from herpes viruses…and whose replication is enhanced by the culprit drug." Pet'r Ex. 28 at 1; *see also* Pet'r Ex. 24 at 9. While all of the articles referenced indicate that a specific pathogenesis of DRESS/DiHS is not known, they all suggest a role for T-cells that are expanded by the drug resulting in large number of cytokines such as tumor necrosis factor (TNF-α) and IFN-γ, leading to symptom manifestation. Pet'r Ex. 24 at 9; *see also* Pet'r Ex. 43 at 5 ("Although the exact pathogenesis is not fully understood"); Pet'r Ex. 36 at 5 ("Although several theories have been proposed, the pathomechanisms of DIHS/DRESS remains largely unknown…The results of patch tests and LTT indicate that drug-specific T cells are behind this syndrome.").

Dr. Rosenstreich also contended that petitioner's event in May 2019 after eating clams was consistent with DRESS. Pet'r Ex. 42 at 5. Dr. Rosenstreich, referencing the Lee article, stated that "up to 25% of cases" have relapses of DRESS that "are often associated with concurrent reactivation of HHV-6." *Id.* He conceded that petitioner's event in May 2019 was not a result of another drug, but by a different type of allergen, the clam protein. *Id.* at 5. However, he still opined that her event in May 2019 was related to her initial influenza vaccine reaction. Pet'r Ex. 42 at 6.

With respect to the timing of petitioner's reaction, Dr. Rosenstreich stated that "the 4-7 days between the vaccination [and dermatological reaction] is consistent with the time it takes to begin activating influenza antigen or drug antigen specific T lymphocytes and expanding the

[7] Lee, Haur Yueh, *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),* Up to Date (online) (2021). [Pet'r Ex. 43].

[8] Tohyama, K, et al., *Association of Human Herpesvirus-6 Reactivation with Flaring and Severity of Drug Induced Hypersensitivity Syndrome,* 157 J. of Derm. 934-940 (2007). [Pet'r Ex. 47 at 1.

clone of these specific cells to a number large enough [to] cause inflammatory symptoms in the skin and other organs." Pet'r Ex. 24 at 11. He referenced a case report by Solak et al., where the patient had received an influenza vaccine and 7 days later developed maculopapular skin rash, facial edema, and eosinophilia. Pet'r Ex. 35 at 1.[9] The authors stated that the allopurinol was being used over a month "but the clinical manifestations appeared 1 week after vaccination application. *Hence, we believe that the viral antigens in the vaccine…might have contributed to trigger the disease." Id.* at 1-2 (emphasis added). Dr. Rosenstreich also referred to a case report by Griffin et al., describing a patient that developed DRESS seven days after receiving an adjuvanted trivalent influenza vaccine. Pet'r Ex. 37[10]; *see also* Resp. Ex. A, Tab 3. The authors wrote, "As an immune stimulant, it makes sense that vaccination could trigger DRESS in certain individuals," and that "the strong temporal relationship between vaccination, onset of symptoms, and the absence of an alternative trigger suggests a role for adjuvanted influenza vaccine as the precipitant of DRESS." Pet'r Ex. 37 at 3. The authors hypothesized that "the vaccine response could facilitate reactivation of latent herpes viruses, as have been implicated in the pathogenesis of DRESS." *Id.* Additionally, Griffin stated, "While the mechanism is unclear, we hypothesis this could be a direct reaction to a vaccine component, or that non-specific immune activation following vaccination could permit a reaction to medication, as postulated in previous cases…" *Id.*

Dr. Rosenstreich concluded both of his reports reiterating his opinion that petitioner did have probable DRESS that was caused by the influenza vaccine. Pet'r Ex. 24 at 11; Pet'r Ex. 42 at 6.

c. Respondent's Expert's Opinion—Dr. Emanual Maverakis

Dr. Maverakis, a dermatologist, opined that petitioner did not experience DRESS, and that the influenza vaccine she received, did not caused her to suffer DRESS, nor did the flu vaccine cause petitioner's reactivation of HHV-6 in 2019. Resp't Ex. A at 17.

With respect to petitioner's diagnosis, Dr. Maverakis stated that petitioner did develop a skin rash after receiving the flu vaccine on September 29, 2016, but that her condition was not DRESS because it lacked clinical signs and symptoms required to make that diagnosis. Resp't Ex. A at 13. Dr. Maverakis, accepting the RegiSCAR diagnostic criterion for DRESS, stated that petitioner's score would be a 3, which is a possible or probable diagnosis of DRESS. *Id.* at 13-14. Specifically, he explained that petitioner did not present with a fever or lymphadenopathy, which are "strong arguments against DRESS." *Id.* at 13. He also acknowledged that petitioner had an abnormal liver function test, showing her ALT level was elevated in her labs on 10/21/2016, but he also observed that petitioner had elevated liver function test results in February 2016, when she had experienced a wild-flu infection. Resp't Ex. A at 13. In his supplemental report, Dr. Maverakis outlined petitioner's lab results from 2015 and 2016, prior to the flu vaccine, which demonstrated mildly elevated ALT and ALK tests. Resp't Ex. B at 5. He

[9] Solak, B. et al., *DRESS Syndrome Potentially Induced by Allopurinol and Triggered by Influenza Vaccine,* BMJ Case Rep. doi:10.1136/bcr-2016-214563 (2016). [Pet'r Ex. 35].

[10] Griffin, D. et al., *A Case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) without a Typical Precipitant,* 212 Med J. Aust. 300-301 (2020). [Pet'r Ex. 37; Resp. Ex. A, Tab 3].

seemingly agreed that her significant elevation in liver function tests in October 2016, could be a sign related to a possible DRESS diagnosis, but argued that since petitioner experienced abnormal liver function tests prior to the vaccination, the abnormal liver function test results were not caused by the flu vaccine. Resp't Ex. B at 4. Dr. Maverakis did not address how petitioner's previous abnormal liver function tests were found during the same time period she had been reporting flu-like symptoms and then found to be positive with influenza A.

Dr. Maverakis' initial report did include some inconsistencies with his evaluation of petitioner's eosinophil levels, as noted by Dr. Rosenstreich, at one time acknowledging that petitioner had elevated levels of eosinophils, but then later stating that "eosinophilia was not noted during her initial presentation." Resp't Ex. A at 13, 15. In his second report, Dr. Maverakis clarified that petitioner's lab from 10/21/2016 did demonstrate eosinophilia and that petitioner's eosinophils were elevated two more times in January 2017. Resp't Ex. B at 4; *see also* Pet'r Ex. 2 at 250, 281.

Finally, Dr. Maverakis acknowledged that petitioner experienced a rash after receipt of the flu vaccine, he argued that the rash was not clearly consistent with DRESS. *Id.* at 13-14. In his supplemental report, Dr. Maverakis conceded that there is no specific characteristics of DRESS rashes, but he argued that petitioner's biopsy's interpretation was that her skin condition was "consistent with a hypersensitivity reaction, such as to an arthropod assault," and that petitioner's biopsy lacked the most commonly found histologic features seen in DRESS rashes. Resp't Ex. B at 5. He referenced an article by Ortonne et al., which examined the histopathological features of DRESS rashes by reviewing skin biopsies of 50 DRESS diagnosed patients and found that the most common dermatological manifestations were "erythroderma, maculopapular rash, bullae/erosive lesions, pustules, and purpura." Resp't Ex. B, Tab 6 at 3.[11] Additionally, Ortonne found that "a diffuse parakeratotic layer" was found in 84% of DRESS patients and infiltrate was only located in the superficial dermis, with the density of inflammatory infiltrates being low or intermediate in the majority of cases. *Id.* at 4. The authors wrote:

> We found that the histopathological presentation of DRESS syndrome is highly variable, encompassing many inflammatory patterns, from a slight perivascular lymphocytic infiltrate to a pustular, AGEP-like, EM-like, eczematous or interface dermatitis, with the latter being the most frequent. What appeared to be a special feature was the association of different inflammatory patterns in a single specimen, a finding that was significantly more frequent in DRESS syndrome that in nondrug dermatoses.

Id. at 7. Despite this, Dr. Maverakis stated, "In short, the most commonly associated features of DRESS were not noted in the biopsy of the petitioner." Resp't Ex. B at 6.

Dr. Maverakis discussed the elevation of HHV-6 titers in petitioner and stated that "nearly everyone in the US population has been infected with HHV-6," and that "reactivation is more common during times of stress, illness, in response to acute allergic reactions, and during immunosuppression." Resp't Ex. A at 14. Even though Dr. Maverakis stated in his report that

[11] Ortonne, N, et al., *Histopathology of Drug Rash with Eosinophilia and Systemic Symptoms Syndrome: A morphological and Phenotypical Study*, 173 Brit. J. of Derm. 50-58 (2015). [Resp't Ex. B, Tab 6]

the HHV-6 reactivation finding was "non-specific," he explained in his supplemental report that that he meant that HHV-6 reactivation is not specific to DRESS, but can be caused by other things, such as the use of immunosuppressants such as corticosteroids. Resp't Ex. A at 14; Resp't Ex. C at 6.

With respect to vaccine causation, Dr. Maverakis opined that the flu vaccine could not have caused DRESS, mostly because there are no epidemiological studies that demonstrate that the flu vaccine could cause DRESS. Resp't Ex. A at 14 ("There are currently no population-based studies linking DRESS to influenza vaccination."). Dr. Maverakis acknowledged the three case reports described the Hewitt, Griffin, and Solak, which Dr. Rosenstreich also referenced, where DRESS followed administration of a flu vaccine, but stated that "it is not surprising, given that by chance, DRESS should sometimes present following an unrelated influenza vaccination." *Id.* Addressing Dr. Rosenstreich's theory of how the flu vaccine could result in DRESS, Dr. Maverakis stated that "expanding T-cells specific to influenza will not cause DRESS….In contrast, T-cell expansion is a very common event…Simply expanding T cells does not cause a cutaneous eruption. In fact, there are skin resident T cells that do not circulate in the periphery and the peripherally expanded T cells do not necessarily track to the skin." *Id.* at 16. In his rebuttal report, without actually addressing how the flu vaccine could cause DRESS, Dr. Maverakis stated that large registries of DRESS patients have failed to find an association between the flu vaccination and DRESS. Resp't Ex. C at 2, citing Resp't Ex. C, Tab 2.[12]

Lastly, addressing the length of petitioner's symptoms, Dr. Maverakis conceded that relapses of DRESS can occur, however, petitioner's alleged "relapses" were not consistent with the relapses described in the medical literature. Resp't Ex. B at 7. He stated that "relapses were most attributed to the introduction of a new medication," and that the relapses present with facial edema, lymphadenopathy, and atypical lymphocytes. *Id.* Dr. Maverakis also acknowledged that DRESS patients could have long-term sequela, including DRESS-induced organ damage, however, petitioner did not have any evidence of such long-term organ damage. Dr. Maverakis disagreed that petitioner's event in May 2019 was a DRESS relapse and noted that petitioner's treating physician did not characterize her event in May 2019 as a DRESS relapse. *Id.*; *see also* Pet'r Ex. 22 at 28.

IV. Analysis

a. Diagnosis

Federal Circuit precedent establishes, in certain cases, it is appropriate to determine the nature of an injury before engaging in *Althen* analysis. *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). Since "each prong of the *Althen* test is decided relative to the injury," determining facts relating to the claimed injury can be significant in a case like this. *Id.* Thus, prior to the inquiry of vaccine causation, the undersigned addresses whether petitioner has established by a preponderance of the evidence that she suffered DRESS.

[12] Kardaun, S.H. et al., *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Original Multisystem Adverse Drug Reaction. Results from the Prospective RegiSCAR study,* 169 Brit. J. of Derm. 1071-1080 (2013). [Resp't Ex. C, Tab 2].

Respondent argues that petitioner has not established by preponderant evidence she suffered from DRESS. Resp't Br. at 15. But he conceded that petitioner developed a skin rash after receipt of the flu vaccine, the diagnosis of DRESS is not supported by the medical records and is inconsistent with the medical literature describing DRESS. *Id.* at 19; *see also* Resp't Ex. A at 13-15. Petitioner, however, asserts that DRESS is the appropriate diagnosis for her condition after receipt of the flu vaccine, as diagnosed by her treating physicians and supported by the opinion of Dr. Rosenstreich. Pet'r Br. at 29-34.

After a review of the medical records, the expert reports, and the medical literature, I find that petitioner has established by preponderant evidence that she developed DRESS and that her injury lasted until August 2017.

Both Drs. Rosenstreich and Maverakis reference the RegiSCAR DRESS criterion outlined above, to diagnose and validate cases of DRESS. Resp't Ex. A at 2; Pet'r Ex. 42 at 3; *see also* Resp't Ex. B, Tab 2. The Shiohara article explains that there is often a delay of DRESS symptoms after introduction of the inciting drug and first symptoms are typically a maculopapular rash with a fever. Pet'r Ex. 29 at 2. DRESS rashes initially present as "patchy erythematous macules, pustular, target-like or eczema-like lesions," that is "symmetrically distributed on the trunk and extremities," with early phase rashes are "periorbital with facial edema with pinhead-sized pustules." *Id.* at 3. Both experts agree that approximately seven days after petitioner received the flu vaccine on September 29, 2016, she developed a rash. *See* Pet'r Ex. 24 at 10; Resp't Ex. A at 13. At petitioner's first emergency room visit on October 10, 2016, the rash was described as "diffuse maculopapular rash over the torso and back, and minimally on the forearms and legs….swelling of the face with erythema and papularity." Pet'r Ex. 8 at 8. The same day, petitioner saw dermatologist, Dr. Kenneth Reed who described petitioner's rash as a "erythematous papular eruption" that distributed on her trunk and neck. Pet'r Ex. 9 at 5. Despite Dr. Maverakis taking issue with the histologic features of petitioner's skin biopsy later, he conceded that petitioner's rash would be consistent with the RegiSCAR rash criteria. Resp't Br. at 19.

Petitioner also presented with elevated eosinophils and abnormal liver function tests, consistent with a DRESS diagnosis. Medical literature submitted by both parties indicate that "transient eosinophilia was far more often present," in DRESS cases than reported. Pet'r Ex. 29 at 4; Resp't Ex. B, Tab 2 at 4. Further, eosinophilia may often be delayed for 1-2 weeks. Pet'r Ex. 29 at 4. Petitioner's labs, taken on October 21, 2016, demonstrated elevated eosinophils and both experts acknowledged this lab finding was consistent with the DRESS RegiSCAR criteria. *See* Resp't Ex. A at 13; Pet'r Ex. 24 at 9. Additionally, petitioner's treating dermatologist, Dr. Geoffrey Yang, considered the elevated eosinophils in petitioner's labs relevant to his diagnosis that petitioner was experiencing a reaction to the flu vaccine. Pet'r Ex. 2 at 86.

Petitioner's abnormal liver function test results are also consistent with the DRESS diagnosis and RegiSCAR criteria. Shiohara, Kardaun, and Cho explain that the liver is frequently affected in DRESS, resulting in elevated liver enzymes. *See* Pet'r Ex 29 at 4 ("elelvated liver enzymes occur in up to 70% of patients with DRESS"); Resp't Ex. B, Tab 2 at 5 ("[m]ost frequently the reaction affected the liver"); Pet'r Ex. 44 at 4 ("Liver injury is the most common type of organ damage and has been found in 75-94% of patients."). Both experts

acknowledged that petitioner's labs on October 21, 2016 did demonstrate abnormal liver function and abnormal liver function test results are consistent with DRESS. *See* Pet'r Ex. 24 at 8; Resp't Ex. A at 13 (petitioner "was found to have a slightly elevated ALT at 133 on 10/21/2016, with the upper limit of normal being 50."). While Dr. Maverakis attempted to minimize petitioner's elevated ALT finding to argue against a DRESS diagnosis because she had previous elevated liver function test results, her previously elevated ALT level occurred while she was found positive for the flu in March 2016, demonstrating that when petitioner's immune system was activated in response to flu antigens, her liver functions became abnormal. Similarly, Dr. Yang also noted petitioner's elevated liver function test results and wrote, "liver involvement is concerning for systemic reaction; will monitor closely." *Id.*

One area of disagreement between the experts with respect to DRESS was the relevance of reactivation of HHV-6 in petitioner. Dr. Rosenstreich explained that DRESS "is frequently associated with reactivation of…human herpes virus 6 ("HHV-6")." Pet'r Ex. 24 at 8. Dr. Maverakis characterized the HHV-6 reactivation as a "non-specific finding," although acknowledging that DRESS patients "will often have activation of HHV-6." Resp't Ex. A at 14. Shiohara, Kardaun, and Sharma all explain that reactivation of "latent viruses," are temporally associated with disease severity and relapse, with HHV-6 being the most commonly identified viral reactivation. Pet'r Ex 36 at 3 ("recent studies, including ours, suggest an intimate relationship between HHV-6 and the development of a severe systemic hypersensitivity syndrome or DRESS."); Pet'r Ex. 48 at 5; Resp't Ex. B, Tab 2 at 5 ("Reactivation of herpes viruses, especially HHV-6, often described in DRESS and even considered a criterion for DIHS by Japanese experts, is held responsible for a more severe and/or protracted course."). Given the medical literature's association of reactivation of HHV-6 and DRESS, it does not appear that this finding is "non-specific" but instead an important consideration for diagnosing and treating a patient with DRESS. In this case, petitioner's labs were remarkable for elevated HHV-6 titers and again, her treating physician, Dr. Yang, also found her elevated HHV-6 titers was an important factor when he diagnosed petitioner with DRESS. *See* Pet'r Ex. 2 at 76.

Importantly, petitioner's treating physicians ultimately diagnosed her with DRESS based on her clinical course and treated her accordingly. When petitioner initial sought treatment for her rash, her physicians associated the rash she developed to the flu vaccine she had received on September 29, 2016. *See* Pet'r Ex. 9 at 6 ("[Patient] just had her [flu] shot, possible reaction to it"); Pet'r Ex. 2 at 86 (Assessment: 1. Rash, likely hypersensitivity reaction to component of flu vaccine.). After reviewing her labs and finding elevated liver function tests, eosinophilia, and HHV-6 reactivation, her dermatologist, Dr. Yang diagnosed petitioner with "likely DRESS from flu shot." Pet'r Ex. 2 at 80. On October 28, 2016, at her second appointment with Dr. Yang, he wrote that she was presenting for a "follow-up of generalized rash, thought likely DRESS from flu shot. Labs remarkable for eosinophilia, HHV-6 of 2300, and ALT of 133….At last visit 1 week ago, patient was started on prednisone 60 mg, along with TAC ointment." *Id.* at 78. His assessment was, "Generalized rash, though likely DRESS from flu shot." *Id.* When petitioner went back to Dr. Yang on December 2, 2016, petitioner's HPI stated, "56-year-old female with DM and DLP who presents to clinic today for follow-up of DRESS (prior symptoms include facial swelling, eosinophilia, elevated ALT, and HHV-6 reactivation on PCR) most likely triggered from influenza vaccine that patient received on 9/26/2016." *Id.* at 56. Dr. Yang also

wrote that petitioner's other medications were not likely the culprit because she had been taking for 1.5 years and "as DRESS usually occurs 1-8 weeks after trigger." *Id.*

Petitioner was also treated with steroids for six weeks, consistent with the consensus treatment for DRESS. *See* Pet'r Ex. 2 at 80. The Shiohara and Mizukawa paper states, "Systemic corticosteroids have been accepted as the gold standard treatment for ameliorating clinical symptoms of DiHS/DRESS at the acute phase….The usual dosage is prednisolone, 40-50 mg/day….tapered over 6-8 weeks to prevent the relapse of various symptoms of this syndrome." Pet'r Ex. 29 at 7. The 2017 Cho article also confirms the long-term use of corticosteroids for a period of 2-3 months. Pet'r Ex. 44 at 13. Additionally, both articles suggest that a gradual taper over a longer duration is preferred to reduce "disease flare-ups" or the development of autoimmune long-term sequelae. *Id.*; *See aso* Pet'r Ex. 29 at 7 ("Once corticosteroids have started, drug dose should be reduced gradually even upon resolution of clinical manifestations. This is because patients with DiHS/DRESS are at greater risk of subsequently developing the wide spectrum of immune reconstitution inflammatory syndrome (IRIS) ranging from CMV disease to autoimmune disease.").

Unfortunately, in this case, petitioner tapered her steroid use faster than what was recommended by her physician, resulting in flare-ups occurring through August 2017. At her appointment with Dr. Yang on December 2, 2016, he noted petitioner "decided to self-taper faster than what we had discussed." Pet'r Ex. 2 at 56. On January 13, 2017, petitioner reported a two-day flare when she woke up with an itchy feeling all over her arms and legs, and she used a cream to resolve the sensation. Pet'r Ex. 2 at 51. When she went to her primary care physician on June 9, 2017, petitioner reported intermittent itching every few weeks and shared a photo of a rash covering her bilateral arms and her thighs. Pet'r Ex. 2 at 123. But by August 2017, at a cardiology appointment, her skin exam was normal. Pet'r Ex. 2 at 41. As a result of petitioner's self-tapering the steroids faster than what was recommended, petitioner experienced flare-ups of her rash and itchiness through August 2017, consistent with what was described in the medical literature. *See* Pet'r Ex. 43 at 7 ("…relapses or flare-ups are common after resolution of the acute disease, occurring in up to 25 percent of cases weeks to months after resolution….Flare-ups tend to be more common in patients treated with systemic corticosteroids and occur more frequently on rapid tapering of corticosteroids.").

However, the records do not support a finding that petitioner's rash and hypersensitivity reaction that occurred in May 2019 was related to her diagnosed DRESS that began in October 2016. On May 2, 2019, petitioner reported to allergist, Dr. Young, that she rapidly developed facial flushing approximately 90 minutes after ingesting clams, then abdominal cramping and loose stools, which resolved overnight. Pet'r Ex. 23 at 3. The following day, petitioner developed hives in a "generalized distribution" and chills in the afternoon and into the evening. *Id.* Petitioner took Benadryl for three days and used an albuterol inhaler, which helped relieve some of the symptoms. *Id.* Petitioner first saw allergist, Dr. Young, who opined that petitioner had a reaction to the clams, stating, "Her constellation of symptoms, especially chills, rhinitis, wheezing, loose stools suggest viral syndrome; presentation for food allergy atypical in terms of symptom onset and the persistence of symptoms." *Id.* at 5.

When petitioner saw Dr. Yang on May 7, 2019, he recounted her history and noted that petitioner ingested clams and "by 5 pm noted hives throughout her body," and she developed wheezing and chills. Pet'r Ex. 22 at 51. Dr. Yang noted that petitioner's blood work demonstrated elevated eosinophils, mildly elevated CRP, and increased HHV-6 titers, but no elevated liver or kidney results. *Id.* By this appointment, petitioner's rash had "mostly resolved and her itch had greatly improved on its own." *Id.* Dr. Yang was able to visualize "excoriated papules on [right] arm x 1 and low back x 1." *Id.* at 53. He diagnosed petitioner with a "rash, favor hypersensitivity reaction based on history, resolving on its own, *I do not suspect DRESS at this time*." *Id.* (emphasis added). Dr. Yang also explained, "Pt's bloodwork was reviewed in detail and I explained that her high eosinophil and elevated CRP can be seen with *any hypersensitivity reaction*," and that he ordered an ECG to help patient "feel reassured," because she had ECG abnormalities during her DRESS episode, but that he "did NOT favor" a DRESS diagnosis at this time. *Id.* at 54. On May 10, 2019, Dr. Yang's office informed petitioner that her labs were remarkable for "HHV-6 and eosinophils," and that petitioner's rash is "likely due to reactive HHV-6," but given no systemic involvement and quick improvement," no action was necessary. *Id.* at 35. When petitioner went to her primary care physician, Dr. Fitzcharles on May 15, 2019, he wrote that petitioner's dermatologist, Dr. Yang, "does not think that this current episode is a recurrence of reactive HHV-6 infection causing DRESS, but instead, as per HHV-6 Foundation to be due to some sort of hypersensitivity reaction to unknown exposure, as current symptoms were not caused by any specific drug or medication (previous symptoms suspected due to preservation additives in influenza vaccine)." Pet'r Ex. 14 at 54.

Even though petitioner's lab work from this period demonstrated elevated eosinophils and a reactivation of HHV-6, Dr. Yang specifically stated that he did not believe that her reaction was associated with her initial DRESS reaction. Further, her presentation of symptom was significantly different from her initial reaction to the flu vaccine in 2016. For example, the onset of her hives was nearly immediately after eating clams, while her rash after the flu vaccine developed approximately seven days later; she developed gastrointestinal issues after eating the clams, and she never experienced gastrointestinal issues after the flu vaccine in 2016; and her rash resolved after taking Benadryl for approximately three days. Finally, even with the elevated HHV-6 PCR finding, the test results narrative explains that, "Rises in antibody titers to HHV-6 have been detected during infection with other viruses. In seroepidemiology studies of the prevalence of exposure using serum screening dilutions of 1:10, the detection of IgG antibody in a mid-life population approaches 100%." Pet'r Ex. 14 at 80. Thus, there is not sufficient evidence to demonstrate that the event in May 2019 was a related to her initial DRESS event occurring in October 2016 after receipt of the flu vaccination.

Based on the evidence summarized above, the undersigned finds that petitioner has proven by preponderant evidence that suffered from DRESS following her flu vaccination and that her symptoms lasted until August 2017.

b. Causation

1. *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*, 451 F.3d at 1355-56. Such theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d 548-49. 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. *See Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). However, a "petitioner must provide a 'reputable medical or scientific explanation' for [her] theory." *Boatmon v. Sec'y of Health and Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Moberly*, 592 F.3d at 1322). While the theory need not be medically or scientifically certain, "it must still be 'sound and reliable'" *Id.* (quoting *Knudsen*, 35 F.3d at 548-49). The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. Causation "can be found in vaccine cases…without detailed medical and scientific exposition of the biological mechanisms." *Knudsen*, 35 F.3d at 548-49.

Dr. Rosenstreich opined that the flu vaccine can cause DRESS by activating T cells, resulting in a multisystem inflammatory reaction. Pet'r Ex. 24 at 9. Dr. Maverakis did not directly dispute Dr. Rosenstreich's theory for the how the influenza vaccine could cause DRESS, he only argued that "expanding T cells specific to influenza will not cause DRESS," and that there are no population-based studies linking DRESS to influenza vaccination. Resp't Ex. A at 14; Resp't Ex. C at 2. For the reasons discussed below, the undersigned finds that petitioner through Dr. Rosenstreich has presented a sound and reliable theory to explain how the influenza vaccine could cause DRESS.

The medical literature filed in this case explains that the pathogenesis of DRESS is not fully understood, but it is thought to be a T-cell mediated hypersensitivity reaction to specific drugs. Pet'r Ex. 43 at 4; *see also* Pet'r Ex. 44 at 10 ("The pathomechenisms of DRESS syndrome are complex and largely unknown."); Pet'r Ex. 36 at 5 ("Although several theories have been proposed, the pathomechanisms of DIHS/DRESS remains largely unknown."). Dr. Rosenstreich opined that the flu vaccine activated T-cells, causing them to release inflammatory cytokines, such as TNF-α and IFN-γ, resulting in the multisystem inflammatory reaction. Pet'r Ex. 24 at 8. Additionally, the Picard et al. article found that DRESS patients had circulating CD8+ T-cells that were activated, exhibited increased cutaneous homing markers, and secreted large amounts of TNF-α and INF-γ. Pet'r Ex. 28 at 2. Further, the articled explained that the "cutaneous and systemic manifestations of an immune response [is] mainly mediated by CD8+ T-lymphocytes directed against herpes virus antigens," which suggests that the "culprit drug may induce reactivation and antigenic presentation of quiescent forms of EBV or other herpes viruses in cells such as B lymphocytes, which could secondarily trigger a multiorgan immune response directed against herpes viruses." *Id.* at 7-8.

The case report by Hewitt, which described a female patient developing DRESS four days after receiving the H1NI vaccine, also endorsed the mechanism of T-cell expansion as a result of the influenza vaccination as the cause of DRESS in the patient. Pet'r Ex. 24 at 3. Even though the patient in the Hewitt case report was also taking sulphasalazine, a known causative agent of DRESS, the patient had been taking that medication for 12 months and it was only after

the introduction of the flu vaccine did the patient develop DRESS. *Id.* at 3. Respondent also filed the case report by Griffin et al., which described an 80-year old male that developed DRESS seven days after receiving the influenza vaccine. Resp't Ex. A, Tab 3. The authors of this care report wrote that the patient's DRESS, "was likely triggered by influenza vaccination." *Id.* at 1. Griffin reiterated that "[t]he pathophysiology of DRESS remains unclear, but it involves an aberrant T-lymphocyte response to an antigen, including drugs and infection." *Id.* at 2. Further, the case report states, "As an immune stimulant, it makes sense that vaccination could trigger DRESS in certain individuals." *Id.* The authors hypothesized that patient's DRESS "could be a direct reaction to a vaccine component, or that non-specific immune activation following vaccination could permit a reaction to medication." *Id.*

Dr. Maverakis only characterizes Dr. Rosenstreich's theory that the influenza vaccine caused a non-specific T-cell activation as "speculative" in both of his reports and does little to refute the theory posited by petitioner. *See* Resp't Ex.A at 16; Resp't Ex. B at 7. Instead, he argued unpersuasively that there are no large-scale population studies that link the influenza vaccine to DRESS, and only a limited number of case reports describing DRESS post-vaccination. Resp't Ex. C at 2. However, the medical literature filed by both parties establishes that the pathogenesis of DRESS if not fully understood and the lack of such research does not defeat petitioner's claim. Moreover, petitioner need not demonstrate a theory by scientific certainty to show that a theory is sound and reliable. *See Knudsen,* 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program."). Further, lack of epidemiological studies is not dispositive. "Requiring epidemiologic studies….or general acceptance in the scientific communities…impermissibly raises a claimant's burden under the Vaccine Act." *Andreu,* 569 F.3d at 1378 (quoting *Capizzano,* 440 F.3d at 1325-26).

Instead, the medical literature described above supports Dr. Rosenstreich's theory for how the flu vaccine can cause DRESS, and accordingly petitioner has demonstrated *Althen* prong one by preponderant evidence.

2. *Althen* Prong Two

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

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. *Andreu,* 569 F3d at 1367; *Capizzano,* 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.' " (quoting *Althen,* 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. *Cucuras,* 993 F. 2d at 1528. While the medical records and opinions of treating physicians must be considered, they are not

binding on the special master. § 13(b)(1)(B) (specifically stating that the "diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court.").

A petitioner need not make a specific type of evidentiary showing, i.e. "epidemiologic studies, rechallenge, the presence of pathological markers o/r genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Capizzano*, 440 F.3D at 1325. Instead, a petitioner may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. *Id.* at 1325-26.

Petitioner has demonstrated by preponderant evidence a logical sequence of cause and effect establishing that the flu vaccine she received on September 29, 2016 the cause of her developing DRESS. Importantly, as discussed above, the undersigned found that petitioner preponderantly established that she developed DRESS and that her symptoms continued until August 2017. Additionally, petitioner proffered a sound and reliable mechanism of vaccine causation.

Moreover, petitioner's various treating physicians provide circumstantial evidence in support of vaccine causation. On October 10, 2016, dermatologist, Dr. Kenneth Reed, assessed petitioner with a "hypersensitivity reaction: erythematous popular eruption distributed on the trunk; *pt just had her flu shot, possible reaction to it*." Pet'r Ex. 9 at 6 (emphasis added). Dr. Yang, petitioner's treating dermatologist at Brigham and Women's Dermatology Department, diagnosed petitioner with "rash, likely hypersensitivity reaction to component of flu vaccine," after his first appointment with her on October 21, 2016. Pet'r Ex. 2 at 90. After reviewing her labs, which were remarkable for elevated eosinophils and liver test results, and HHV-6 titers, Dr. Yang revised his diagnosis of petitioner to "Generalized rash, thought likely DRESS *from flu shot*," and he also noted that petitioner had been on "HCTZ and Synthroid…and Lipitor" for a long period of time that those drug were "extremely unlikely [to be] the culprit, as DRESS usually occurs 1-8 weeks after trigger." Pet'r Ex. 2 at 69, 75. At petitioner's third appointment on November 8, 2016 with Dr. Yang, he again revised his diagnosis of petitioner to "DRESS, most likely from flu shot," and in describing petitioner's history, he wrote, "…pleasant 56-year old female with DM and DLP who presents today for a [follow-up] of DRESS (prior symptoms include facial swelling, eosinophilia, elevated ALT, and HHV-6 reactivation on PCR)*most likely triggered from influenza vaccine that patient received on 9/29/16.*" *Id.* at 69 (emphasis added). Most importantly, Dr. Yang explicitly explained that petitioner's other drugs were not likely the cause of her developing DRESS, as she had been on them for a long-period of time. These statements, individually and collectively, constitute circumstantial evidence that petitioner's treating physicians associated the flu vaccine she received on September 29, 2016 with the development of her DRESS.

Dr. Maverakis acknowledged that petitioner developed a rash approximately one week after the flu vaccine, along with eosinophilia, abnormal liver function tests, and HHV-6 reactivation, but opined that it was a possible combination of petitioner's age and a history of elevated IgE that caused her "pruritic skin eruptions." Resp't Ex. A at 14. Aside from suggesting that it was not the flu vaccine that caused petitioner to develop a rash, and other signs and symptoms consistent with DRESS, he does not suggest an alternative cause for the sudden onset of these symptoms approximately seven days post-vaccination.

As petitioner has provided a sound and reliable mechanism to explain how the flu vaccine could cause DRESS, petitioner developed DRESS in the manner described in the medical literature, and her treating physicians associated her condition to the flu vaccine, petitioner has provided preponderant evidence of a logical sequence of cause and effect establishing that the flu vaccine caused her DRESS, and has satisfied *Althen* prong two.

3. *Althen* Prong Three

Althen prong three requires petitioners to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen,* 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." *Id.* Petitioners must offer "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan,* 539 F.3d at 1352. The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under *Althen* prong one). *Id.*; *see also Pafford,* 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. *See e.g. Veryzer,* 100 Fed. Cl. at 356 (explaining that a "temporal relationship alone will not demonstrate a causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury.").

Dr. Rosenstreich opined that the onset of petitioner's DRESS, approximately 4–7-day post-vaccination is consistent with "the time it takes to begin activating influenza antigen or drug antigen specific T lymphocytes and expanding the clone of these specific cells to a number large enough to cause inflammatory symptoms in the skin and other organs." Pet'r Ex. 24 at 11. The three case reports where patients developed DRESS after the flu vaccine all developed their symptoms between 4-7 days post-vaccination. *See* Resp't Ex. A, Tab 3 at 1 (patient received the flu vaccine 7 days prior to DRESS symptom onset); Pet'r Ex. 34 at 1 (onset of rash, lymphadenopathy, and fever 4 days post-H1N1 vaccination); Pet'r Ex. 35 at 2 (onset of maculopapular skin rash, facial edema, and dysuria seven days after receiving an influenza vaccine). Additionally, the medical literature describing DRESS explains that usually there is a delay of symptom onset between receipt of the "offending drug" and symptoms. *See* Pet'r Ex. 43 at 4 ("The latency phase (from drug initiation to onset of reaction) typically ranges from two to eight weeks."); Pet'r Ex. 29 at 3 (Th disease usually starts abruptly with maculopapular morbilliform exanthema with fever….2-3 weeks after the introduction of the culprit drug.").

Dr. Maverakis agreed that petitioner's rash began one week post-vaccination, however, since the majority of his opinion was focused on petitioner's diagnosis, he did not provide an opinion as to whether the development of her rash occurred in a medically acceptable timeframe for her symptoms to begin. *See* Resp't Ex. A at 2; Resp't Ex. B at 2 ("a temporal relationship between her rash and an influenza vaccine a few days prior is not sufficient evidence to conclude…that the vaccine caused her skin rash.").

Petitioner received the influenza vaccine on September 29, 2016 and she went to the emergency department on October 10, 2016 stating that she developed a "rash seven days ago,"

that was on her back and torso and developed to facial edema and "papularity."). Pet'r Ex. 6 at 20. Petitioner consistently reported this timeframe of symptom onset to her providers, who associated the onset of her rash to the flu vaccine. *See* Pet'r Ex. 6 at 33-36; Pet'r Ex. 2 at 59-62.

The onset of petitioner's symptoms and the symptoms she experienced was consistent with the three case reports where patients developed DRESS symptoms 4-7 days post-vaccination. Additionally, the delayed onset of her symptoms was consistent with the DRESS diagnosis, as described in the medical literature, and supported by her treating physicians. Therefore, the undersigned finds that petitioner has preponderantly established *Althen* prong three.

V. Conclusion

In accordance with the above, petitioner has established by preponderant evidence that she is entitled to compensation, having demonstrated that the flu vaccine she received on September 29, 2016 was the cause-in-fact of her developing DRESS from which she suffered through August 2017. A separate damages order will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master