In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: October 8, 2025

TERESA LANDRUM,	*	
Petitioner,	*	No. 18-1497V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Phyllis Widman, Widman Law Firm, LLC, Linwood, N.J., for petitioner.
Alec Saxe, U.S. Department of Justice, Washington, D.C., for respondent.

DECISION[1]

On September 28, 2018, Teresa Landrum ("petitioner") filed her claim in the National Vaccine Injury Compensation Program[2], alleging that as a result of receiving the influenza ("flu") vaccine on October 27, 2015, she suffered Mast Cell Activation Syndrome ("MCAS"), along with a "significant aggravation/exacerbation of arthritis, rheumatoid arthritis with associated polyneuropathy, small fiber neuropathy, exacerbation of carpel tunnel syndrome, urticaria, flushing/nausea episodes, dermatitis, upper extremity numbness, Raynaud's syndrome, anaphylaxis, and a right shoulder injury. Petition (ECF No. 1); Amended Petition (ECF No. 81). After a review of the record, I find that petitioner has not established by preponderant evidence she is entitled to compensation, and this petition shall be **DISMISSED.**

[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.

I. Procedural History

Petitioner filed her claim alleging that the flu vaccine she received caused her to develop many different injuries, including mast cell activation syndrome. Petition. Accompanying her claim were medical records, an affidavit, and proof of vaccination. *See* Petitioner ("Pet.) Exhibits ("Exs.") 1-11 (ECF Nos. 7 & 8). Between October 2018 and July 2019, petitioner continued supplementing the record with additional medical records and her Worker's Compensation Claim. *See* Pet. Exs. 12-22.

On October 3, 2019, I held a recorded status conference at which I ordered petitioner to file additional medical records to support evidence of a cognizable injury and then to file an expert report to support petitioner's vaccine causation claim. *See* Scheduling Order (ECF No. 27). Complying with the order, petitioner filed additional medical records and an expert report by treating physician Dr. Jonathan Bernstein.[3] Pet. Exs. 23-28.

I held another status conference on April 24, 2020, and ordered petitioner to file a supplemental expert report and set a deadline for respondent to file a responsive expert report. Scheduling Order (ECF No. 42). Petitioner filed a supplemental expert report from Dr. Bernstein on May 11, 2020. Pet. Ex. 38 (ECF No. 47). Petitioner also filed an additional report from Dr. Bernstein regarding petitioner's diagnosis. *See* Pet. Exs. 44 & 49. I held a third status conference on June 30, 2021, at which I ordered petitioner to file an expert report regarding petitioner's allegation that the flu vaccine caused her to develop her alleged injuries. Scheduling Order (ECF No. 65). On November 1, 2021, petitioner filed an expert report from Dr. Omid Akbari.[4] Pet. Ex. 54.

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[3] Dr. Jonathan Bernstein is a practicing allergist at the Bernstein Allergy Group/Clinical Research Center and Professor of Medicine at the University of Cincinnati College of Medicine. Pet. Ex. 50 at 1. He received his medical degree from the University of Cincinnati College of Medicine in 1985 and performed a Fellowship in Allergy and Immunology at Northwestern University. *Id.* Dr. Bernstein is licensed to practice medicine in Ohio, Indiana, and Kentucky. *Id.* Dr. Bernstein has been teaching at the University of Cincinnati College of Medicine since 1990 and also works at the Cincinnati Children's Hospital Medical Center. *Id.* at 6. Dr. Bernstein teaches allergy fellows in research and clinical care and supervises third- and fourth-year medical students and residents. *Id.* at 7. He has served as a reviewer for many medical journals including Annals of Allergy, Asthma and Immunology, and Allergy. *Id.* Dr. Bernstein has been the primary author or co-author on numerous articles regarding allergies and allergic-type reactions, including urticaria, vasculitis, dermatitis, and chronic rhinitis. *Id.* at 7-36. Dr. Bernstein is an expert in allergy and immunology, and he has provided expert reports in other cases before the VICP. *See e.g. Mulrenin ex rel. R.M. v. Sec'y of Health & Hum. Servs.,* No. 18-22V, 2021 WL 566441 (Fed. Cl. Spec. Mstr. Jan. 19, 2021).

[4] Dr. Omid Akbari is currently a Professor of Immunology and Medicine at the Keck School of Medicine, University of Southern California. Pet. Ex. 54; Pet. Ex. 112. Dr. Akbari received his Ph.D. in Cellular and Molecular Immunology from the National Institute for Medical Research in 1998. Pet. Ex. 112 at 1. He did a postdoctoral fellowship at Stanford University from 1999-2001. *Id.* Dr. Akbari previously performed research at Stanford University in the Division of Allergy and Immunology and became a tenured Professor of Immunology at the Keck School of Medicine, University of South California in 2008. *Id.* at 2. He has served as a reviewer for the National Institute of Health and served as a reviewer for many journals, including Nature Immunology, Journal of Immunology, The Journal of Rheumatology, and Nature Medicine, among others. *Id.* at 5. Dr. Akbari has been the author or co-author of numerous medical articles in the field of immunology. Pet. Ex. 54 at 2. Dr. Akbari has testified and written reports in other VICP cases as an expert in immunology.

Respondent filed expert reports from Drs. Soman Abraham[5] and Dr. Chester V. Oddis[6], along with supporting medical literature. *See* Respondent ("Respt) Exs. A & C. On July 5, 2022, respondent filed the Rule 4(c) report, recommending against compensation. Respt Report ("Rept.") (ECF No. 79). In response to respondent's expert reports, petitioner filed responsive supplemental expert reports. Pet. Exs. 52 & 54. Respondent also filed responsive expert reports from Dr. Abraham. Resp't Ex. E (ECF No. 95).

On October 13, 2023, petitioner filed a status report requesting the Court set deadlines to resolve petitioner's claim on the record. Pet. Status Rept. (ECF No. 97). Accordingly, petitioner filed this motion for a ruling on the record on December 18, 2023. Pet. Mot. (ECF No. 98). Respondent filed a response to petitioner's motion on March 3, 2024. Respt Response (ECF No. 102). Petitioner has not filed a reply.

I have determined that the parties have had a full and fair opportunity to present their cases and that it is appropriate to resolve entitlement in this matter on the existing record. *See* Vaccine Rule 8(d); *see also Kreizenbeck ex rel. C.J.K. v. Sec'y of Health & Hum. Servs.,* 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record"). Accordingly, this matter is now for adjudication.

II. Legal Standard

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-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

[5] Dr. Soman Abraham is a Grace Kerby Distinguished Professor of Pathology in the Department of Pathology at Duke University in Durham, North Carolina. Resp. Ex. A at 1; Resp. Ex. B at 1. After completing his undergraduate and master degrees at Ahmadu Bello University in Zaria, Nigeria, Dr. Abraham received his Ph.D. from the University of Newcastle Upon Tyne, in the United Kingdom in 1981. Resp. Ex. B at 1. He completed his post-doctoral research training at the University of Tennessee in 1986 and begun his teaching career in microbiology and immunology shortly thereafter. *Id.* Beginning in 1997, Dr. Abraham became a professor of Pathology at Duke Medical Center and continued to teach until present. *Id.* at 2. Dr. Abraham has served as a Board Member for many different medical publications, including the Journal of Microbiology and Frontiers in Bioscience. *Id.* Dr. Abraham has published numerous peer reviewed articles on the topic of mast cell biology and function as the primary author or as a support author. *Id.* at 15-30. Dr. Abraham is the primary or co-investigator for research funded by NIH. *Id.* at 12-13. Accordingly, he is admitted as an expert in the field of pathology and mast cell biology and function.

[6] Dr. Chester Oddis is the Director of the Myositis Center at the University of Pittsburgh Medical Center. Resp. Ex. D at 1. He received his medical degree from Pennsylvania State University in 1980 and completed his fellowship in Rheumatology at the University of Pittsburgh, School of Medicine in 1987. *Id.* He is licensed to practice medicine in the State of Pennsylvania and is board certified in Internal Medicine and Rheumatology. *Id.* at 3. After completing his fellowship, Dr. Oddis began teaching as a Professor in the Rheumatology and Clinical Immunology division at the University of Pittsburgh School of Medicine. *Id.* at 2. He became the Director of the Rheumatology Fellowship Training Program in 2001 and became the Director of the Myositis Center in 2010. *Id.* Dr. Oddis has been the lead author or co-author on numerous medical publications in the field of rheumatology. *Id.* at 3-15. Dr. Oddis serves as a grant reviewer for various grant review committees, including for NIH and he has served as a manuscript reviewer for multiple medical publishers, including Journal of Clinical Rheumatology and Journal of Rheumatology. *Id.* at 41. Dr. Oddis is accepted as an expert in the field of rheumatology and immunology.

certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

In the present case, petitioner does not allege a Table injury. Rather, she alleges that flu vaccine she received on October 27, 2015, was the "cause-in-fact" of her development of mast cell activation syndrome ("MCAS") giving rise to a wide variety of signs and symptoms which occurred over the succeeding years. Pet. Mot. at 1. Thus, she bears the burden of establishing actual causation.

To prove causation-in-fact, the petitioner must "show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination and 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." *Althen v. Sec'y of Health & Human Servs.,* 418 F. 3d 1274, 1278 (Fed. Cir. 2005). There must be preponderant evidence for each *Althen* prong. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam,* 463 Fed. Appx. 932 (Fed. Cir. 2012).

The preponderance of the evidence standard requires the petitioner to demonstrate that it is "more likely than not" that the vaccine caused the injury. *Moberly v. Sec'y of Health & Human Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner must demonstrate that the vaccine was "not only [a] but for cause of the injury but also a substantial factor in bringing about the injury." *Moberly,* 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.,* 135 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Pafford v. Sec'y of Health and Human Servs.,* 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation is determined on a case-by-case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.,* 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon "circumstantial evidence" which is consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen,* 418 F. 3d at 1280.

If the petitioner makes a *prima facie* case supporting vaccine causation-in-fact, the burden shifts to respondent to show by a preponderance of the evidence that the injury is instead due to factors unrelated to the administration of the vaccine. *Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). Respondent has the burden of demonstrating that: "[A] factor unrelated to the vaccination is the more likely or

principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury. If the evidence or alternative cause is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen*, 35 F.3d at 551.

Additionally, medical records are generally considered trustworthy. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F. 2d at 1525, 1528 (Fed. Cir. 1993). Where medical records are clear, consistent and complete, they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs.*, No. 03-1585V, 2005 WL 6117475 (Fed. Cl. Spec. Mstr., Dec. 12, 2005). Medical records may be outweighed by testimony that is given later in time that is "consistent, clear, cogent, and compelling." *Camery v. Sec'y of Health & Human Servs.,* 42 Fed. Cl. at 381, 391 (1998).

If there is a dispute as to the nature of the petitioner's injury, the special master may opine on the nature of the petitioner's injury." *Contreras v. Sec'y of Health & Human Servs.,* 844 F. 3d 1363, 1368 (Fed. Cir. 2017) (citing *Hibbard v. Sec'y of Health & Human Servs.,* 686 F. 3d 1355 (Fed. Cir. 2012); see also *Broekelschen v. Sec'y of Health & Human Servs.,* 618, F.3d 1339 at 1346 (Fed. Cir. 2010). In *Broeklschen,* the Federal Circuit stated that it was appropriate for the special master to first determine which injury is best supported by the evidence presented in the record before applying the *Althen* test. *Broekelschen* at 1346.

III. Evidence Submitted

a. Summary of Petitioner's Medical Records

1. Pre-Vaccination Medical History

Prior to the vaccination, petitioner had a history of being treated for fatigue, diarrhea, hypertension, syncope, flushing, chest pain, nausea, vomiting, abdominal pain multiple incidents of respiratory illnesses, seasonal allergies and other non-specific symptoms. This summary of the medical records is focused on the records that detail symptoms most relevant to petitioner's diagnosis of hereditary alpha tryptasemia ("HαT") with mast cell activation syndrome.

Following an emergency department visit for dizziness, lightheadedness and vertigo, petitioner had an appointment on June 30, 2013, with her primary care physician, Dr. Steven Morton. Pet. Ex. 11 at 412. Petitioner reported that the onset was sudden and that the symptoms occurred intermittently. *Id.* Petitioner also described that she had a headache which was associated with nausea, vomiting, numbness and tingling and weakness. *Id.* She returned to her PCP on July 2, 2013 for a follow-up from her tests and at this appointment, in addition to a headache, fatigue and weakness, petitioner also reported nasal congestion associated with postnasal drainage, ear fullness and pressure in her cheek. *Id.* at 393. Petitioner was diagnosed with acute sinusitis and an acute upper respiratory infection. *Id.* at 396. She was given a course of antibiotics. *Id.*

Petitioner went back to Dr. Morton on July 18, 2013, for "an evaluation and management of syncope," and explained that she had about four episodes of syncope that were associated with

"dyspnea and flushing." Pet. Ex. 7 at 387. Petitioner also reported excessive fatigue and malaise. *Id.* Under "Assessment and Plan" petitioner was diagnosed with syncope and referred to a cardiologist. Her complaints of malaise and fatigue, diarrhea, and arthralgias, among other issues were noted. *Id.* at 390. Dr. Morton also ordered labs for petitioner's hypertension, arthralgia, and diarrhea. *Id.* at 1980. Petitioner's antinuclear antibodies were negative, but her stool sample was positive for lactoferrin. The record states, "a positive result is an indicator of intestinal inflammation." *Id.* at 376.

Petitioner saw cardiologist Dr. Loventhal on August 16, 2013. Pet. Ex. 11 at 383. He wrote, "[Petitioner] is a pleasant 40-year-old nurse who has had three episodes of chest discomfort over the last year. These are described as hot, burning, epigastric and low retrosternal discomfort with radiation to both arms associated with nausea. The last one was about one month ago, and she became diaphoretic[7] with it. These episodes come and go for about a minute and half at a time." *Id.* at 383. Dr. Loventhal noted that petitioner had "active gastroesophageal reflux disease." *Id.* An echocardiogram showed occasional heart palpitations. *Id.* at 385.

On January 9, 2014, petitioner saw Dr. Morton for an illness three weeks in duration. Pet. Ex. 11 at 367. Petitioner reported that she started vomiting at work and was sent home. *Id.* Petitioner also stated that she has had nasal congestion for three days associated with dizziness, facial pain, fever and vomiting. *Id.* Petitioner was diagnosed with a cold and sinusitis. *Id.* She was prescribed prednisone and Cetrizine. *Id.* at 371.

On January 20, 2014, petitioner underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy65[8], and cystourethroscopy. Pet. Ex. 7 at 1642. Petitioner had been experiencing pelvic pain, which was caused by a fibroid and a right ovarian dermoid. *Id.*

Petitioner saw Dr. Charles Sewall, an ENT, on March 26, 2014 for "significant bouts of bi-temporal headaches and some watery discharge from both ears." Pet. Ex. 11 at 365. His impression was, "combination of chronic rhinitis with secondary eustachian tube dysfunction and external otitis." *Id.* He prescribed her EC-Naprosyn for "general anti-inflammation" and ordered skin tests to determine if she had any allergies. *Id.* Again, result of these tests were not included in the record. Aside from prescription refills, there are no additional records with Dr. Morton until December 30, 2014, when petitioner presented with blisters in her throat. Pet. Ex. 11 at 358. Petitioner had a negative strep test. *Id.* She was given a prescription for penicillin. *Id.*

On January 2, 2015, petitioner was diagnosed with a sore throat and she restarted a Medrol pack and given a throat wash. *Id.* at 355. On January 23, 2015, petitioner had a CT chest for "superficial swelling" and the impression was, "The largest right axillary lymph node measures 1.3 cm without other evidence of lymphadenopathy." Pet. Ex. 7 at 1566. She had a repeat sonogram of her chest, and the impression was "enlarged lymph nodes within the right

[7] Excessive sweating.

[8] Removal of both ovaries and fallopian tubes.

axillary region. Compared to previous 01/19/2015 study these are grossly stable in size. Grossly stable enlarged right axillary region lymph nodes that appear otherwise normal." *Id.* at 1546.

Petitioner had an appointment with Dr. Susanne Sparklin for "fatigue," on April 8, 2015. Pet. Ex. 7 at 1534. Dr. Spranklin had petitioner's TSH levels, along with testosterone and progesterone levels tested. *Id.* at 1535. Tests revealed that petitioner had a slight Vitamin D deficiency.

On August 7, 2015, petitioner presented to Dr. Morton for an upper respiratory infection, where petitioner described symptoms of nasal congestion, sore throat and hoarseness. *Id.* at 342. Petitioner reported that her symptoms occur "constantly," and she also had associated symptoms of ear plugging, headache, facial pressure, and swollen lymph nodes. *Id.* She was again diagnosed with an acute upper respiratory infection and sinusitis. *Id.*

On August 21, 2015, petitioner presented to Baptist Health Center for lab tests for symptoms of "burning with urination/low back pain." Pet. Ex. 7 at 1517. Lab results showed that petitioner had a high white blood cell count in her urine and trace bacteria was detected. *Id.* at 7. However, there are no additional corresponding records for this lab order.

Petitioner presented to Baptist Health on October 20, 2015 for a cough and congestion. Pet. Ex. 7 at 1509. She had an X-ray of her chest, which was normal. *Id.* at 1511. Again, there are no other corresponding records with this medical appointment from Baptist Health or from her primary care physician, Dr. Morton.

2. Post-Vaccination Medical Records Between October 27, 2015 and December 2018

On October 27, 2015, petitioner received her flu vaccine at her place of employment. Pet. Ex. 1. The same day, at 3:28 pm, petitioner went to the emergency department at Baptist Health Corbin, complaining of moderate, itchy skin rash with generalized distribution, and trouble swallowing. Pet. Ex. 7 at 1489. Petitioner was given an IV of methylprednisolone and Benadryl in the emergency department. *Id.* at 1493. At 5:00 pm, Nurse Gross re-assessed petitioner and found that petitioner responded well to the medication administered and was cleared for discharge. *Id.* Petitioner was diagnosed with "generalized allergic reaction with skin rash and hives secondary to [intramuscular drug] and flu vaccination." *Id.* at 1487.

On October 30, 2015, petitioner reported to occupational medicine, reporting that she had an adverse reaction to the flu vaccine two minutes after it was administered. Pet. Ex. 22 at 5.

On December 11, 2015, forty-four days after the vaccination, petitioner went to the Pineville Community Hospital emergency department with right flank pain and vomiting. Pet. Ex. 9 at 115. Petitioner reported that these symptoms began three hours prior to coming to the hospital. *Id.* She returned to the emergency department on December 29, 2015, this time with a sore throat, earache, and head congestion with white nasal discharge. *Id.* at 107. She had pain over her maxillary sinuses when tapped on and tonsillar erythema. *Id.* at 108. Petitioner was given a prescription of antibiotics and diagnosed with sinusitis. *Id.* The following day, on

December 30, 2015, petitioner returned to the Pineville Community Hospital for an evaluation of a sore throat. Pet. Ex. 3 at 24. Petitioner reported that the sore throat "has been going on for the past several days" and that even with oral antibiotics, petitioner was experiencing a significant amount of drainage. *Id.* Petitioner was admitted to the hospital for further evaluation. *Id.* The Cytomegalovirus test results indicated that petitioner had an elevated IgG and equivocal IgM result. *Id.* at 22-23. Petitioner was treated with IV Unasyn and given a mouth rinse and diagnosed with bilateral purulent pharyngitis, odynophagia, elevated liver functions, and hypertension. Pet. Ex. 9 at 99.

Petitioner had a follow-up appointment with Dr. Combs-Woolum on January 29, 2016. Pet. Ex. 3 at 10. At this appointment, petitioner reported that she was doing better after her hospitalization and that she had blood work, but they did not do an Epstein Barr Virus test. *Id.* Petitioner stated, "She did have the flu shot. Feels some of her problem originated after the flu vaccine." *Id.* Petitioner's recent blood work showed elevated liver function and hyperlipidemia. *Id.*

On March 28, 2016, petitioner went to the Baptist Health Laboratory to provide a urine sample due to burning with urination. Pet. Ex. 7 at 1459. Then on April 18, 2016, Dr. Michael T. White, diagnosed petitioner with "fatigue" and ordered a complete blood cell count for petitioner and complete metabolic panel. *Id.* at 1450. The record from this lab request also has "Magnesium/Fatigue" under "Miscellaneous." *Id.* Petitioner's glucose was elevated to 105 mg/dL. *Id.* at 1452. There are no other records associated with these lab tests or Dr. White.

On April 29, 2016, petitioner presented to the Pineville Community Hospital emergency department with vomiting, coughing, and a feeling that she was about to pass out. Pet. Ex. 9 at 84, 93. The admitting physician, Dr. Madhan Mohan wrote that petitioner's shortness of breath had begun two-days prior, and that the petitioner had a low-grade fever. *Id.* at 83. It was noted that petitioner was in "mild respiratory distress" in the emergency department and a chest x-ray showed "bronchitic changes." *Id.* at 84. She was admitted and started on "intensive bronchial therapy" along with IV antibiotics and steroids. *Id.* at 92. She was discharged on May 2, 2016 with diagnosis of "COAD[9] exacerbation with failed outpatient therapy; acute chronic sinusitis; hypertension; palpitation secondary to albuterol treatment." *Id.*

Two days after her discharge, petitioner returned to Pineville Community hospital with acute diarrhea and abdominal pain in the right lower quadrant. Pet. Ex. 9 at 80. A CT scan of petitioner's abdomen was normal, with a showing of smooth appearance of the wall of the left colon, sigmoid, and rectum possibly related to colitis. *Id.* at 72. Petitioner was given an antiemetics and IV fluids and discharged with a diagnosis of "colitis probably antibiotic induced c.diff colitis." *Id.* at 78. On May 9, 2016, petitioner had a follow-up appointment with Dr. Combs-Woolum for the recent hospitalization. Pet. Ex. 3 at 9. Dr. Combs-Woolum noted that petitioner finished the Medrol dose pack and was negative for diarrhea. *Id.* Petitioner indicated that she could not tolerate Zoloft and she felt as if her thyroid was enlarged, as she was experiencing fatigue. *Id.* Dr. Combs-Woolum noted that petitioner had "some soft tissue swelling around the anterior cervical region bilaterally." *Id.* Petitioner's diagnosis was "lower

[9] COAD- Chronic Obstructive Airway Disease

respiratory tract infection; fatigue; lymphadenopathy," and Dr. Combs-Woolum ordered a CBC, throat culture, and thyroid tests. *Id.*

Two and half months later, on July 24, 2016, petitioner went back to Pineville Community Hospital with symptoms of abdominal pain and right flank pain. Pet. Ex. 9 at 58. Petitioner reported that she was having nausea and diarrhea that started five hours before. *Id.* Under "Exacerbating Factors" "fatty foods" was listed. *Id.* Petitioner was given Toradol and IV fluids for hydration, and discharged to home with a diagnosis of gastroenteritis. *Id.* at 64.

On August 5, 2016, petitioner had an appointment with Dr. Combs-Woolum for chronic sinusitis. Pet. Ex. 3 at 8. The note indicated that petitioner was "taking Augmentin 875 mg" and that petitioner had "finished a Medrol pack," after failing multiple over-the-counter medications. *Id.* Petitioner also started a probiotic. *Id.* Dr. Combs-Woolum referred petitioner to an allergist, Dr. Sewel and made a note about petitioner's gallbladder. *Id.*

On September 1, 2016, petitioner went to the emergency department of Baptist Health Corbin with "vasovagal-like symptoms and nausea and vomiting." Pet. Ex. 7 at 129. Petitioner stated that she has had a 20-pound weight loss that started "3 to 4 weeks ago." *Id.* Petitioner indicated that she was scheduled to see Dr. Jobson for an outpatient appointment but started vomiting and having chills. *Id.* Petitioner was admitted for further evaluation. *Id.* During her hospitalization, petitioner was evaluated by Dr. Jimmye Perkins, and petitioner reported to him that her first vasovagal episode was five years ago at a baseball game after she finished eating and "she had a feeling in her stomach that felt like a shock wave; a warm and funny feeling, as well as tingling; then she had nausea, turned cold and clammy, and then passed out briefly." *Id.* at 137. Petitioner also reported, "Then a couple of years ago, she was traveling in a car and had just eaten 30-45 minutes prior. She had the same warm and fuzzy feeling in her abdomen, in the same clamminess; this time she did not pass out but felt lightheaded." *Id.* Dr. Perkins reviewed petitioner's chest exams and EKGs and wrote, "I am not sure at this time what is causing the patient's symptoms. For the syncope and pre-syncope, I'm going to monitor her on telemetry and obtain a heart echo…. Her symptoms [are] almost like irritable bowel syndrome." *Id.* at 142. Petitioner also had a consult with Dr. Brenda Jobson, gastroenterologist, while hospitalized. *Id.* at 143. During this consultation, petitioner reported having right upper quadrant abdominal pain and an abnormal weight loss of 20 pounds. *Id.*

Dr. Jobson scheduled an esophagogastroduodenoscopy and reviewed petitioner's CT scan from Pineville Community Hospital. *Id.* at 150. Dr. Jobson's differential diagnosis was carcinoid, pheochromocytoma, and possible serotonin syndrome. *Id.* Dr. Jobson noted that the "[m]ost common cause may be that [petitioner] has severe constipation," and ordered MiraLAX for petitioner. *Id.* Petitioner was discharged on September 3, 2016, and the discharge summary noted that the EGD found esophagitis and gastritis. *Id.* at 134. The "Hospital Course" also explained that while hospitalized petitioner began to have another "episode" and tried Ativan which resolved petitioner's anxiousness and syncope episode. *Id.* The same section states, "The patient suggested herself that these episodes may be panic attacks; she noticed that when the nursing staff [stayed] in the room with her and talked to her, she did better. She also noted that the Ativan seemed to improve and abort the [syncope] attack." *Id.* at 134-35.

On September 14, 2016, petitioner had a follow-up appointment with Dr. Jobson. Pet. Ex. 7 at 335. Dr. Jobson performed a colonoscopy which was positive for mild chronic gastritis with focal minimal neutrophilic activity and the esophagus biopsy showed minimal chronic esophagitis. *Id.* at 369. Petitioner had an appointment with Dr. Combs-Woolum on September 30, 2016 for a hospital follow-up and this record is mostly illegible. Pet. Ex. 3 at 4. Dr. Combs-Woolum noted that petitioner had started on Lorazepam. Petitioner also reported that she was experiencing "diarrhea as well as constipation," but that it was constipation a majority of the time. *Id.* Petitioner also reported to Dr. Combs-Woolum that "all of this started after her flu vaccination." *Id.* Dr. Combs-Woolum diagnosed petitioner with "weight loss, nonspecific abdominal pain, pharyngitis, and dizziness." *Id.*

On October 5, 2016, petitioner sought treatment at Surfside Beach Primary Medical for hives. Pet. Ex. 10 at 2. Petitioner reported that she has a rash that started on her wrist and spread while she was in the sun. *Id.* When petitioner returned from vacation, she had an appointment with Dr. Combs-Woolum on October 10, 2016. Pet. Ex. 3 at 1. Dr. Combs-Woolum noted that petitioner was taking Prednisone, Zyrtec, Zantac, and Benadryl. *Id.* Petitioner was still having the rash when she saw Dr. Combs-Woolum. *Id.* Petitioner also reported that she received a Celestone[10] shot in the emergency department which did help. *Id.* Dr. Combs-Woolum observed a macular popular rash on petitioner's abdomen and legs and referred her to an allergist. *Id.*

Petitioner had a skin biopsy performed on October 12, 2016. Pet. Ex. 11 at 341. The biopsy, taken from her abdomen, showed "superficial perivascular and interstitial infiltrate of neutrophils, lymphocytes, eosinophils, histiocytes, and mast cells with dermal edema." *Id.* Leukocytosis vasculitis was not appreciated. *Id.* The diagnosis was "findings most consistent with urticaria." *Id.*

On October 25, 2016, petitioner had an appointment with Dr. Mansoor Ahmed, a rheumatologist, for a rash. Pet. Ex. 6 at 16. Petitioner reported that the onset of the rash was a few weeks ago and was ongoing. *Id.* Petitioner also complained of low energy and fatigue and seasonal allergies. *Id.* Dr. Ahmed recorded that petitioner had a "reddish macular rash" on her neck, chest, back, abdomen and upper extremities. *Id.* at 17. He also wrote that petitioner was positive for anti-chromatin antibody, but her ANA was negative. *Id.* at 18. Dr. Ahmed wrote that petitioner's skin biopsy was consistent with urticaria.

The same day, petitioner had an appointment with allergist, Dr. Brandi Dyer, for hives and swelling. Pet. Ex. 11 at 337. Petitioner reported that the rash began the first week in October 2016 on vacation at the beach. *Id.* She stated that "any piece of skin covered with her swimsuit was not affected and strangely her lower extremities were not either," but she also had face and lip swelling. *Id.* Petitioner had urticaria on her face, neck, chest, arms, and legs. *Id.* The hives appear as soon as she wakes up and goes away by the time she goes to bed. *Id.* Despite taking Benadryl, Cetirizine (Zyrtec) and Prednisone, her symptoms occur daily. *Id.* Petitioner stated that she's "never had any symptoms like this before." *Id.* Petitioner also told Dr. Byer that she had been evaluated by an ENT in September, and she was positive for cat, dust mite, trees, grasses and ragweed allergens and that she has a "history of an adverse reaction to

[10] Celestone is the brand name for betamethasone a topical steroid.

the influenza vaccine last year." *Id.* at 338. Petitioner stated that "for 2-3 weeks after this reaction, she was having daily coughing, wheezing, and shortness of breath," and that after the reaction to the flu vaccine, she was "hospitalized for tonsillitis around Christmas 2015 and hospitalized again in April 2016 for pneumonia." *Id.* Additionally, petitioner reported that a skin biopsy from her abdomen was "consistent with urticaria and no vasculitis was noted." Pet. Ex. 16 at 244.

Dr. Dyer assessed petitioner with allergic rhinitis, allergic conjunctivitis, acute urticaria, recurrent infections, allergic reaction with a history of an immediate reaction post-influenza vaccine last year. *Id.* Dr. Dyer wrote:

> [Petitioner] is a complicated individual with multiple issues at this time. She was referred due to a history of acute urticaria. She understands that given her history, feel that there is not a specific trigger for her symptoms. 25% of people sometime in their life will have an episode of hives for no reason. She has already had a big workup in the last 3 weeks since these symptoms started. She is seeing a rheumatologist today, but [does] not feel that her symptoms are likely due to a drug induced lupus. She understands that the treatment of urticaria is to block histamine release.

Id. at 339. Petitioner was given a prescription for an inhaler, and a nasal spray. *Id.*

Petitioner saw Dr. Morton on October 25, 2016 at Grace Health Falls Highway Clinic. Pet. Ex. 11 at 333. The "History of Present Illness" indicated that petitioner was complaining of an "allergic reaction" and that she had experienced hives after the flu vaccine last year. *Id.* Petitioner stated that she developed "similar symptoms on October 3, 2016, with an allergic reaction-hives/rash/shortness of breath." *Id.* She still has a rash and itching, but it is only in sun exposed areas. *Id.* Dr. Morton diagnosed petitioner with acute urticaria and noted she saw an allergist earlier in the day and was started on Prednisone and antihistamine. *Id.*

Petitioner went to the emergency department at UKHealthcare on October 29, 2016 for "generalized rash and angioedema since early October...has finished course of antibiotics and symptoms not greatly improved." Pet. Ex. 13 at 3. The "History of Present Illness" stated:

> 43 [year old] female who presented on 29 October 2016 with several week history of generalized burning pruritic rash that she states began after visiting Myrtle Beach…Patient had recently seen allergist and rheumatologist this week and has been on 2 weeks of prednisone and Benadryl and Pepcid for the rash. Patient states that the rash [does] resolve by evening she wakes up every morning and the rash returns.

Pet. Ex. 13 at 7. Petitioner was given Benadryl and Pepcid in the emergency department and the was "observed for several hours and patient symptoms improved with no facial swelling." *Id.* at 8. Additionally, the attending physician wrote, "[It] is unclear what is causing patient's symptoms may be allergic reaction versus rheumatologic rash manifestation. She [states] symptoms were likely exacerbated today by use of ibuprofen yesterday." *Id.* Petitioner's tryptase level was taken and it was 16 and noted as "abnormally high." *Id.* at 14.

On November 7, 2016, petitioner had a telehealth appointment with Dr. Brandi Dyer of Family Allergy & Asthma. Pet. Ex. 16 at 229. Dr. Dyer reviewed petitioner's lab work, including her CBC and told petitioner that "there was some mild abnormalities in [red blood count] indices and a mild increase in neutrophils and mild decrease in lymphocytes," and that petitioner had "a low TSH, but normal T3 and T4. Negative thyroid autoantibodies." *Id.* Dr. Dyer wrote, "[Patient] understands that there is no concrete reason to explain her recent symptoms. She is concerned that her TSH is low when it was high in the past….She will likely need her thyroid studies in about 6 weeks….She understands that her tryptase was elevated, indicating that her increase in symptoms may have been due to a reaction-likely due to ibuprofen." *Id.* Petitioner reported being "hive free for about five days," and that she had been weaning the prednisone and was weaning antihistamines. *Id.*

The next evening, on November 8, 2016, petitioner went to Pineville Community Hospital with intractable nausea. Pet. Ex. 9 at 29. Petitioner had vomiting and diarrhea, accompanied by mild epigastric pain and had multiple episodes of emesis. *Id.* A CT of her abdomen showed "the presence of very dilated fluid filled small bowel loops consistent with significant ileus." *Id.* at 19. Acute gastroenteritis was suspected. *Id.* She was diagnosed with "acute gastroenteritis" and "intractable nausea and vomiting." She was given IV fluids and Flagyl and discharged after feeling "much better." *Id.* at 23.

Petitioner had an appointment at Family Allergy and Asthma on November 16, 2016, with Dr. Rajiv Arora. Pet. Ex. 11 at 321. Petitioner explained she had an episode of angioedema, which was thought to be related to taking ibuprofen and her tryptase level was elevated to 16. *Id.* Petitioner also said she was taking prednisone and tapering down but having breakthrough urticaria. *Id.* She had also been hospitalized for a gastrointestinal infection. *Id.* Petitioner reported having significant sinus pressure of moderate intensity for the past month. Dr. Arora wrote, "[Petitioner] continues to have active urticaria despite multiple meds, including prednisone. She is essentially at the point of chronic urticaria and has had an episode of angioedema after taking ibuprofen. Although this may be chronic idiopathic urticaria/angioedema, I am concerned another underlying process since she reports a 30 lb. unexplained weight loss prior to onset of the urticaria and an elevated tryptase during the episode of angioedema. *Id.* at 322. He prescribed petitioner a course of Augmentin and indicated that petitioner would trial Xolair.[11] *Id.*

On December 28, 2016, petitioner had a sick visit at Family Allergy & Asthma for a "skin rash after taking Bactrim for a sinus infection and bronchitis." Pet. Ex. 16 at 188. Petitioner reported that she had been diagnosed with bronchitis two days ago and given a course of Bactrim, but developed facial redness. *Id.* at 189. The "History of Present Illness" from this appointment notes that petitioner was taking Zantac and Singular and that she received a Xolair injection on December 19th, and had joint and muscle pain the following day, which was "now improving" and she had "no recent urticaria." *Id.* at 189. Petitioner's problem list included, "allergic rhinitis: perennial with seasonal triggers; allergic conjunctivitis: chronic; reactive

[11] Xolair is an IgE blocker that is administered by subcutaneous injection and is used to treat a number of allergic conditions.

airway disease; urticaria: idiopathic, chronic; drug reaction: adverse history of immediate reaction after influenza vaccination last year; pruritis; recurrent infections." *Id.* at 190. Dr. Arora noted that petitioner "had not had recent urticaria," but was on Xolair, which was helping and that petitioner had recurrent infections and ordered a full immune system evaluation. *Id.*

The panel revealed that petitioner had a normal range of anticardiolipin IgM and negative anticardiolipin IgG, her complement total was low at 33, and her antibody levels (IgG, IgM and IgA) were all within normal levels. Pet. Ex. 16 at 162. However, her protection against various types of pneumoniae antigens were low, but Dr. Arora wrote that these results were "not surprising." *Id.* at 157.

Petitioner returned to Dr. Mansoor Ahmed on January 3, 2017 for a follow-up appointment with a "non-specific rash on her upper body." Pet. Ex. 6 at 13. The record indicates that the onset of the rash was "a few months ago," and it was described as chronic. *Id.* The physical examination revealed petitioner had diffuse tenderness in her upper shoulders and in her bilateral knees. *Id.* at 14. Additionally, petitioner's skin examination showed a "reddish maculo-papular rash" on her left trunk, upper and lower extremities. *Id.* Dr. Ahmed diagnosed petitioner with idiopathic urticaria, "other vasculitis limited to the skin," polyarthritis, and raised antibody titer. *Id.*

On January 16, 2017, petitioner had a follow-up with Dr. Rajiv Arora for her allergic rhinitis and urticaria and Xolair injection. Pet. Ex. 16 at 154. Petitioner reported some improvement from her last appointment, and she finally felt that her sinus infection improved after a course of Levofloxacin. *Id.* Petitioner's urticaria had improved, but some facial flushing and itching remained. *Id.* Petitioner received the Pneumovax vaccine at this appointment. *Id.* at 156. He also observed that petitioner benefitted from Xolair and her present treatment would continue. *Id.*

Petitioner returned to Dr. Arora on February 27, 2017 for another Xolair injection and check-up. Pet. Ex. 16 at 149. Under "HPI" it noted that petitioner's hives were well controlled by Xolair, but was experiencing some hair loss and joint pain since the injections began. *Id.* Petitioner reported having a "mild episode" of hives on her upper arms the day before, but had improved. *Id.* Given the side effects of Xolair, Dr. Arora suggested that the injections stop and monitor for a recurrence of the urticaria. *Id.* at 151.

At the beginning of March 2017, however, petitioner's hives returned on her hands, ankles, and feet. Pet. Ex. 16 at 145. Petitioner explained she was given a prescription of prednisone. *Id.* Petitioner called again on March 15, 2017, indicating that she was experiencing hives and hot flashes with tachycardia. *Id.* at 119. The note indicated that she had yet to fill the prescription of prednisone, but had been taking both Claritin and Allegra. *Id.* On March 20, 2017, petitioner reported that she was having breakthrough hives with the prednisone taper and wanted to know if she could re-start the Xolair shots. *Id.* at 111.

On May 13, 2017, petitioner went to the emergency department at Pineville Community Hospital for hives. Pet. Ex. 9 at 13. The symptoms were described as a "red rash, typical of early symptoms of [patient's] chronic idiopathic urticaria and recurring angioedema." *Id.* The

onset was described as "on and off for years. Just finished prednisone dose pack 2 days ago…rash may be rebound effect from stopping steroid." *Id.* The skin exam revealed "mildly, red, flat (except mildly raised facial) macular patchy areas of upper torso, neck, facial, bilateral upper extremity." *Id.* at 16. Petitioner was given a 60 mg tab of prednisone and her symptoms were marked as "improved." *Id.*

On June 2, 2017, petitioner went to Dr. Morton at 4:01 pm for labs and a follow-up for care after she went to the emergency department earlier in the morning for chest pains. Pet. Ex. 11 at 255. Dr. Morton wrote that petitioner had a rash and that her urticaria was not getting any better. *Id.* at 258. He referred her to Cleveland Clinic Allergy. *Id.*

On June 5, 2017, petitioner received another Xolair injection from Dr. Arora. Pet. Ex. 11 at 253. Dr. Arora wrote that petitioner "has had more than just urticaria" and had "frequent occurrences of erythematous papules and flat erythema on her face/neck." *Id.* He noted that she was experiencing frequent arthralgias and myalgias, along with chest pain. *Id.* Dr. Arora agreed with an evaluation of her at the Cleveland Clinic because "I have no evidence of immune deficiency or allergies as the cause" and that her situation was "no longer looking like chronic idiopathic urticaria." *Id.* at 254. Petitioner received a Xolair shot and Dr. Arora wrote, "Regarding further evaluation-will check 24-hour urine histamine and PGD2 for possible mast cell activation syndrome but would keep evaluating for other causes." *Id.*

Ten days later, on June 15, 2017, petitioner went to the Baptist Health Emergency Department for shortness of breath, along with numbness and tingling in both hands and feet. Pet. Ex. 7 at 923. Petitioner was also experiencing nausea and vomiting. *Id.* Petitioner reported to Nurse Jones that she had been experiencing "hot flash symptoms with light-headedness since receiving the flu shot in 2015," and that the "episodes are intermittent." *Id.* Petitioner was discharged to home. *Id.*

Petitioner had a consult with Dr. Aaron House on June 13, 2017 for possible right axillary lymphadenopathy. Pet. Ex. 7 at 247. Dr. House wrote, "Currently, I feel no palpable lymphadenopathy in the right axilla, but the patient does state she has fullness in this area." *Id.*

Petitioner had a dermatology appointment with Dr. Samuel Pruden on June 22, 2017. Pet. Ex. 4 at 1. Petitioner reported having skin issues since October 2017 and they have been present for the past nine months. *Id.* Dr. Pruden noted that petitioner did not have any present urticaria and recommended that she continue her current treatment plan. *Id.*

The following day, on June 23, 2017, petitioner was evaluated at the Cleveland Clinic by Dr. Jaclyn Bjelac. Pet. Ex. 15 at 1. Petitioner reported, "she was well until she experienced an episode of anaphylaxis due to influenza vaccine October 27, 2015…and within 5 minutes developed lightheadedness, pre-syncopal, sensation of throat closure, nausea. No rash, emesis, or other systemic symptoms." *Id.* Petitioner also reported "recurrent episodes of urticaria which began October 2016 while vacationing at the beach." *Id.* Additionally, petitioner also reported "separate episodes, describes as sensation of lip and tongue swelling, sensation of flushing, nausea, GI upset, "hot flash all over my body," and she has gone to the ER multiple times. A erythematous rash persists several days after these episodes with possible triggers including heat

and stress. *Id.* Petitioner also reported Raynaud's of the hands and feet that began a few months ago, along with issues with memory and fatigue. *Id.* Dr. Bjelac wrote that petitioner's possible diagnoses include chronic idiopathic urticaria and possible mast cell disorder, but noted that her tryptase levels were normal during flushing episodes making mast cell less likely. *Id.* at 5. Dr. Bjelac recommended that petitioner have a repeat skin biopsy and consider a double-blind placebo-controlled trial of omalizumab injections given concerns for arthralgias. *Id.*

Petitioner saw Dr. Arora on July 12, 2017 for her Xolair injection. Pet. Ex. 11 at 235. Petitioner felt flushed and lightheaded after receiving the injection but laid down and symptoms resolved. *Id.* He noted that petitioner had several other "non-specific complaints" including "itching, rashes, joint pain, swelling, fatigue, decreased visual acuity, and worsening memory." *Id.* After an examination he wrote:

> [Patient] continues to have multiple non-specific complaints. We retried Xolair because of perceived benefit. She has had current joint pains with restarting. She has multiple other complaints….these would not go along with chronic idiopathic urticaria. She needs evaluation for other causes-she has pending rheumatology appointment. Also recommend a skin biopsy of any future active lesion. Will get a tryptase today and with any future episodes. There has been concern for mast cell activation syndrome. She contacted NIH and I spoke with Dr. Milner there-he was concerned about MCAS, but there has been no objective evidence to confirm. She had one elevated tryptase during an episode of symptoms after taking a NSAID…otherwise, all other tryptases including during symptoms have been negative. 24-hour urine histamine and PGD2 have been negative.

Id. The plan was to continue petitioner's present treatment, but to decrease her Singulair dosage. *Id.* Petitioner's tryptase level was tested on July 12, 2017, which was found to be within normal range (11.8 with normal range being 2.2-13.2 ug/L). Pet. Ex. 16 at 47.

On August 10, 2017, petitioner had a repeat skin biopsy from her right foot which showed "focal acute vasculitis within the superficial dermis with scattered eosinophils most suggestive of a drug reaction." Pet. Ex. 4 at 29.

Petitioner went to the emergency department of Baptist Health on August 11, 2017 for severe abdominal pain, nausea, and vomiting. Pet. Ex. 7 at 1080. The physical exam of her abdomen revealed that she had a positive Murphy's sign, an indication that petitioner's gallbladder was inflamed. *Id.* She was diagnosed with "generalized abdominal pain" and "hypokalemia." *Id.* at 1083.

Petitioner was initially evaluated by Dr. Bernstein on August 19, 2017. Pet. Ex. 11 at 230; Pet. Ex. 14 at 36. Petitioner told Dr. Bernstein that she had been experiencing urticaria "since October" and that in October 2015 she had an anaphylaxis event related to the flu vaccine. *Id.* Petitioner reported that during the anaphylaxis event she experienced "dizziness, dry mouth, difficulty swallowing, rash," and that she gets similar episodes every 1-5 months. *Id.* Petitioner also reported that she had tried Xolair injections without benefit, Dapsone without help, and had extensive blood work which was normal. Pet. Ex. 14 at 38. She reported that her recent skin

biopsy mentioned vasculitis and necrosis, and her autoimmune workup was negative. *Id.* Dr. Bernstein diagnosed petitioner with urticarial vasculitis and was going to review her biopsy slides, prescribed petitioner Sulfasalazine twice a day and hydroxychloroquine. *Id.*

On August 28, 2017, petitioner had an appointment at Family Allergy and Asthma for "fatigue, vision changes, rashes, breathing symptoms, and 'puffiness.'" Pet. Ex. 16 at 25; *see also* Pet. Ex. 11 at 227.

Petitioner had a follow-up with Dr. Bernstein on September 12, 2017 and reported having "urticarial breakouts on a daily basis since October 2016," and that she was in the emergency department five days ago for hives and difficulty swallowing. Pet. Ex. 14 at 34. Petitioner stated that she "wakes up with hives every morning," and "gets vomiting with episodes and night sweats." *Id.* Petitioner stated that a prednisone taper appeared to be helping. *Id.* Dr. Bernstein confirmed that the most recent skin biopsy confirmed mild leukocytoclastic vasculitis and wrote as the assessment, "44-year-old female with history of leukocytoclastic vasculitis-neutrophilic infiltrate associated with fibrin deposition-attributes reaction to flu vaccine." *Id.* at 35. Dr. Bernstein prescribed Cyclosporine to suppress petitioner's immune system.

On September 15, 2017, petitioner had an appointment with Dr. Morton and reported that her medication, the Cyclosporin, had improved her urticaria but was causing nausea, vomiting, and weakness. Pet. Ex. 11 at 220. Dr. Morton prescribed petitioner Ondansetron, to take as necessary for nausea. *Id.* at 223.

Petitioner had a telehealth appointment with Dr. Bernstein on October 21, 2017, and she reported that she had not had hives since September 30th and was taking a prednisone taper. Pet. Ex. 14 at 31. Additionally, she reported tolerating the Cyclosporin, but had more flushing and her knuckles to the tips of her fingers get red and purple and painful. *Id.* Dr. Bernstein recommended petitioner seek treatment from an ophthalmologist and suggested that she may need a nerve conduction study to evaluate her neuropathy. *Id.* at 32. Additionally, he ordered more blood tests. *Id.*

Petitioner had an appointment with Dr. Morton on November 2, 2017 for a "follow-up of hives" and she reported she was "much better and pleased with progress." Pet. Ex. 11 at 180. Dr. Morton did note petitioner's right axillary lymph node was enlarged and tender. *Id.* at 183.

Petitioner had another telehealth appointment with Dr. Bernstein on November 18, 2017. Pet. Ex. 14 at 26. Petitioner reported that she currently had a red rash on her cheeks with slight swelling. *Id.* Additionally, she told Dr. Bernstein that her toes and fingers "felt frost bit" and she was having nausea, which she was attributing to her gallbladder. *Id.* She was also experiencing "a lot of joint pains in her hands, legs, and back." *Id.* Dr. Bernstein diagnosed petitioner with urticaria vasculitis with neutrophilia, told her to stop Sulfasalazine and to continue her other medication. *Id.* at 28. He noted that her last blood work showed she had a slightly elevated CRP and ESR, but normal cANCA and pANCA. *Id.*

On December 29, 2017, petitioner went to the emergency department at Baptist Health Corbin. Pet. Ex. 7 at 1286. Petitioner reported that she was working with a patient, removing a

chemotherapeutic agent and bag, noticed that the bag had an odd smell, and she began to have flushing, facial swelling, and right sided facial tingling. *Id.* Petitioner was diagnosed with an allergic reaction and acute sinusitis. *Id.* at 1289.

3. Petitioner's Medical Records from 2018 through 2021

On January 2, 2018, petitioner had an appointment at Baptist Health Gastroenterology for heartburn. Pet. Ex. 11 at 146. Petitioner reported that she has fluctuations between diarrhea and constipation. *Id.* PA Chasteen reviewed petitioner's imaging of her abdomen and noted that the radiologist's impression was "no definitive source for patient's symptoms," as her liver, spleen and adrenal glands all appeared normal. *Id.* Petitioner endorsed fatigue. *Id.* Petitioner was diagnosed with gastroesophageal reflux disease. *Id.* at 150.

Petitioner returned to Dr. Ahmed on January 18, 2018. Pet. Ex. 6 at 6. She endorsed fatigue, sleep disturbances, and low energy, along with intermittent skin rashes. *Id.* Petitioner had diffuse tenderness in her bilateral upper extremities and "widespread tender points" in her bilateral lower extremities. *Id.* at 7. Dr. Ahmed diagnosed petitioner with polyarthritis, idiopathic urticaria, rash and other nonspecific skin eruption, and vasculitis limited to skin. *Id.*

Two days later, on January 20, 2018, petitioner had a telehealth appointment with Dr. Bernstein. Pet. Ex. 14 at 22. Dr. Bernstein noted that petitioner was on cyclosporin and HI/H2LTMA for leukocytoclastic vasculitis. *Id.* at 24. Petitioner was experiencing headaches and swelling of her feet, but no rashes since starting the cyclosporin. *Id.* Petitioner also reported no vomiting or diarrhea, but headaches in the base of her head. *Id.* Dr. Bernstein recommended that petitioner decrease her dosage of cetirizine and cyclosporin and trial amitriptyline for her headaches. *Id.* at 25.

On February 5, 2018, petitioner went to Dr. Morton for a follow-up labs and treatment for a tension headache. Pet. Ex. 11 at 135. Dr. Morton noted that petitioner had a rash and bilateral cervical tenderness and muscle spasms. *Id.* Petitioner also demonstrated tenderness on the right upper quadrant of her abdomen. *Id.* at 137. Dr. Morton diagnosed petitioner with cervical paraspinal muscle spasms and malaise and fatigue. *Id.* at 138.

Petitioner had an appointment with Dr. Morton on March 27, 2018 for sore throat, congestion, low-grade fever, chills, weakness, and malaise. Pet. Ex. 11 at 106. Petitioner had ear pain, nasal congestion, sore throat, and difficulty breathing on exertion. *Id.* at 108. She was diagnosed with an upper respiratory infection and given a prescription for Augmentin. *Id.* Petitioner also received the Tdap vaccine at this appointment. *Id.*

Dr. Morton wrote a note, dated April 23, 2018, which stated, "[Petitioner] with prior adverse reaction after flu vaccine. Please excuse her from any further vaccine for flu." Pet. Ex. 1 at 96.

On May 12, 2018, petitioner had a telehealth appointment with Dr. Bernstein and petitioner reported she was having breathing issues and was getting dizzy and flushed. Pet. Ex. 14 at 18. She stated that the amitriptyline did not help her headaches. *Id.* The skin inspection

indicated that petitioner had a rash and "flushing of face with possible hive lesions." *Id.* at 19. Dr. Bernstein recommended that petitioner continue Sandimmune and reduce the dosage of Zyrtec. *Id.* Additionally, he recommended that petitioner get a SNAP study or sleep study. *Id.*

Petitioner returned to Dr. Ahmed, rheumatologist, on May 15, 2018. Pet. Ex. 6 at 2. Petitioner had a nonspecific rash, described as "chronic." *Id.* He noted that petitioner was taking Cyclopsporin and wrote, "If Dr. Bernstein wishes to stop Cyclosporin she can be started on other DMARDS ("Disease modifying Anti Rheumatic Drugs"). I have asked her to get me the records from him. *Id.* at 4.

Petitioner had an appointment with Dr. Bernstein on June 23, 2018 for a follow-up of her chronic hives and leukocytic vasculitis. Pet. Ex. 14 at 15. Petitioner reported having "severe pain," but it was "better since on prednisone." *Id.* She also still had flushing. *Id.* Dr. Bernstein noted that petitioner was tapering her cyclosporin and Dr. Ahmed wants to start petitioner on MTX for joint pain. *Id.* Dr. Bernstein recommended that petitioner continue to taper her cyclosporin and taper the prednisone. *Id.* at 16. He also diagnosed petitioner with "diffuse arthritis." *Id.*

On July 3, 2018, petitioner went to Dr. Morton for "diffuse aches and pains and malaise." Pet. Ex. 11 at 59. She reported tapering down on the Cyclosporin and was having "mild exacerbations" and weakness, myalgias, rash and joint aches and pains "related to autoimmune condition." *Id.* Dr. Morton referred petitioner to a cardiologist for chest pain and shortness of breath; referred her for a sleep study; recommended adding Fosamax for her chronic steroid use. *Id.* at 62.

Petitioner went to dermatologist, Dr. Pruden on July 12, 2018, for skin lesions on the left calf, right cheek, and left cheek. Pet. Ex. 4 at 3. Dr. Pruden described the lesions as "asymptomatic and moderate in severity," and present for six years. *Id.* Dr. Pruden noted that petitioner was diagnosed with chronic urticaria and being treated by Dr. Bernstein for vasculitis. *Id.* Dr. Pruden diagnosed petitioner with "solar lentigines on the right medial [cheek] and left crus of helix,"; "seborrheic keratosis on the left cavum concha;" and dermatofibroma on the superior lumbar spine; left anterior distal upper arm, and right medial proximal pretibial region." *Id.* Dr. Pruden explained that solar lentigines can resolve with sunblock or sun avoidance, and that lentigines "are benign pigmented lesions that occur on sun-exposed and sun-damaged skin." *Id.* Additionally, he treated her seborrheic keratosis and removed the neoplasm on her left cheek. *Id.*

Petitioner had an appointment with cardiologist Dr. Pramod Reddy on July 27, 2018. Pet. Ex. 11 at 37. Dr. Reddy wrote that petitioner was having "recurrent episodes of chest pain and tightness and pressure over the last 3-4 months." Pet. Ex. 11 at 37. Petitioner described the chest pain as "mild intensity" and 2-3/10 on the pain scale. *Id.* The History of Present Illness also stated, "She has severe shortness of breath, nausea and vomiting. She reports intermittent episodes of palpitations with rapid heartbeat with flushing and elevated blood pressure periodically." *Id.*

On August 8, 2018, petitioner went to Grace Health Falls Highway Clinic for 6-7 episodes of vomiting and not feeling well. Pet. Ex. 11 at 18. Petitioner reported that she had a "flushing feeling" in the early morning. *Id.* She also endorsed chills, lightheadedness, and constipation associated with her vomiting. *Id.* Petitioner also reported having right ear pain, sinus pain, and vertigo. *Id.* at 19. She had tenderness over her sinuses. *Id.* at 21. Petitioner was diagnosed with acute sinusitis and given a Medrol tapering pack along with Augmentin. *Id.* at 22.

The following day, August 9, 2018, petitioner had a telehealth appointment with Dr. Bernstein. Pet. Ex. 11 at 15; *see also* Pet. Ex. 14 at 10. Petitioner reported that her musculoskeletal pains went away on a higher dose of Cyclosporine but she was being assessed for gallbladder issues. Pet. Ex. 14 at 10. Dr. Bernstein wrote that petitioner's urticaria vasculitis was "well controlled on cyclosporine," and the plan was to start to taper her down over a six-week period. *Id.* at 12. Petitioner also reported that she had an appointment with a surgeon for an evaluation of her gallbladder. *Id.*

Petitioner had an in-person appointment with Dr. Bernstein on September 12, 2018 for a flare up of her urticarial vasculitis. Pet. Ex. 14 at 6. Petitioner had been tapering down the Cyclosporin and had to go back up to 200 mg a day because at 25 mg every other day, she experienced diffuse hives all over her body. *Id.* Petitioner also reported having associated flushing, nausea and vomiting and diarrhea. *Id.* Petitioner also told Dr. Bernstein that she "relates the urticarial vasculitis from the flu shot." *Id.* At this appointment, petitioner had diffuse urticarial rash all over her lower extremities, along with diffuse redness over her arms and abdomen. *Id.* at 8. Dr. Bernstein got a skin biopsy from her legs and diagnosed her with urticarial vasculitis. *Id.* at 9. The result of the skip biopsy was "unremarkable epidermitis and dermis without infiltrate or vasculitis." Pet. Ex. 17 at 36.

Petitioner had a follow-up appointment with Dr. Bernstein on November 3, 2018. Pet. Ex. 17 at 3. Dr. Bernstein wrote that petitioner's "rash, itching, hives, and flushing" were "all gone." *Id.* Petitioner was only experiencing severe joint pain. *Id.* He also wrote, "All labs were normal as was the biopsy." *Id.* Dr. Bernstein noted that petitioner had been diagnosed with strep and given a five-day course of antibiotics.

On November 14, 2018, petitioner went to the emergency department of the Middlesboro ARH Hospital for nausea, vomiting, and diarrheal episodes that had lasted 6-7 hours prior to arrival. Pet. Ex. 20 at 55. Petitioner associated these symptoms with her urticarial vasculitis. *Id.* Petitioner was given IV fluids and steroids, and her symptoms appeared to improve. *Id.* at 56.

Petitioner had a telehealth appointment with Dr. Bernstein on December 15, 2018. Pet. Ex. 19 at 16. Dr. Bernstein wrote that petitioner's last cyclosporin level was normal and her kidney function was normal. *Id.* Petitioner reported that prednisone was the only medication that was helping with her joint pain and flushing. *Id.* He gave her an order to get a bone density scan to assess for osteopenia/osteoporosis and diagnosed her with urticarial vasculitis and chronic urticaria. *Id.* at 16.

On January 9, 2019, petitioner had another appointment with Dr. Bernstein to fill out the Asthma and Rhinitis Questionnaire and have a follow-up for her urticarial vasculitis. Pet. Ex. 19 at 12. Petitioner reported having no joint pain or muscle aches with 5 mg of prednisone daily. *Id.* Petitioner reported getting hot flashes periodically. *Id.* Dr. Bernstein diagnosed petitioner with diffuse arthritis that was better on prednisone and urticarial vasculitis. *Id.*

Petitioner went to Middlesboro Hospital's emergency department on January 16, 2019 complaining of dizziness and vomiting. Pet. Ex. 20 at 74. Petitioner reported that she has vasculitis and "bouts of vomiting" that only resolves with Solumedrol. *Id.* She was given a saline IV, along with an IV of methylprednisolone. *Id.* at 77. Her vomiting subsided and she was discharged with a diagnosis of vasculitis, and nausea and vomiting. *Id.* at 76.

She went back to the emergency department on January 20, 2019 for abdominal pain. Pet. Ex. 20 at 90. Petitioner noted that she was scheduled to have her gallbladder removed on February 8th, but she was experiencing right flank pain. *Id.* at 87. She was diagnosed with acute gastritis, abdominal pain, vasculitis, nausea and vomiting, and right upper quadrant pain. *Id.* at 89.

Apparently, petitioner had her gallbladder removed in February 2019, as she reported to the emergency department and to Dr. Bernstein. *See* Pet. Ex. 19 at 7. On April 6, 2019, petitioner had an appointment with Dr. Bernstein and she reported that her urticarial vasculitis (had improved) "especially since gallbladder was removed." *Id.* He wrote that she was a 46-year-old woman with urticarial vasculitis and was "doing well." *Id.* at 9. He ordered her to get a bone density scan and to continue prednisone, but try to taper off.

Between April 8th and 18th, petitioner went to Dr. Morton three times complaining of diarrhea and stomach pain. Pet. Ex. 18 at 16-30. On April 18, 2018, Dr. Morton informed petitioner that she was positive for c=diff and noted that this was her fourth time in the year she has tested positive for it. *Id.* at 30. He referred petitioner to a gastroenterologist. *Id.* at 35.

On April 28, 2019, petitioner went to the emergency department of Middlesboro Hospital complaining of vomiting, diarrhea, abdominal pain and muscle spasms. Pet. Ex. 20 at 123. She reported that in February 2019, she had a cholecystectomy to remove her gallbladder. *Id.* Petitioner also reported that she was being treated for c.diff and had two days left of treatment. She was diagnosed with gastroenteritis and discharged to home.

Petitioner returned to Dr. Bernstein on May 21, 2019 for a follow-up for her urticarial vasculitis. Pet. Ex. 19 at 4. He wrote, "Onset about two years ago but is now more frequent. Reports of symptoms nausea, dizziness, flushing episode, vomiting, feeling faint, heart rate and blood pressure increased….Note that all this started one year *after* she had an anaphylactic reaction to influenza vaccine." *Id.* (emphasis added). He wrote, "episodes more frequent when the prednisone taper is finishing." *Id.* Petitioner was going to have a TILT table test to rule out POTS. *Id.* Dr. Bernstein opined that petitioner had "possible mast cell disorder" and wanted to check her serum tryptase, 24-hour urine methylhistamine, and urine PGF2alpha. *Id.* at 5. Petitioner's TILT table test, performed on July 17, 2019, was normal. Pet. Ex. 23 at 2, 13.

Petitioner was evaluated by gastroenterologist, Dr. Kathleen Martin on June 17, 2019. Pet. Ex. 23 at 8. The "History of Present Illness" states that petitioner "has had c.diff 4 times in a year." *Id.* Petitioner reported that her first episode of c.diff was in 2016 and she related her c.diff to cyclosporin, but she had stopped the cyclosporin in February. *Id.* Petitioner also reported that her immunologist thinks she has IBS because of her alternating diarrhea, constipation, abdominal cramping and bloating. *Id.* Additionally, petitioner started the low FODMAP diet, but was not strict about following it. *Id.* Dr. Martin diagnosed petitioner with abdominal cramping and GERD, and recommended that petitioner stop using antibiotics, try to stop taking Dexilant and only use Ranitidine. *Id.*

On September 14, 2019, petitioner returned to Dr. Bernstein for a follow-up. Pet. Ex. 24 at 4. Petitioner's biggest complaints were joint pain. Dr. Bernstein noted that petitioner had an elevated tryptase level when tested on June 14, 2019 and her chromogranin A was also elevated. *See* Pet. Ex. 43 at 23. He diagnosed her with mast cell disorder, disorder of autonomic nervous system, urticarial vasculitis, arthritis, and irritable bowel syndrome. Pet. Ex. 24 at 5.

Between September 27, 2019 and December 20, 2019, petitioner sought treatment for nausea, urinary tract infection, fatigue, and upper respiratory infections. *See* Pet. Ex. 53 at 204-219.

Petitioner had a telehealth appointment with Dr. Bernstein on January 18, 2020. Pet. Ex. 37 at 10. Petitioner reported having reactions to foods, but no further rashes. *Id.* Additionally, petitioner was experiencing joint swelling and pain. *Id.* Dr. Bernstein wrote, "Associates all of her reactions to anaphylaxis to the flu vaccine. Claim is MCAS is caused by the flu shot. Off prednisone currently." *Id.* Dr. Bernstein diagnosed petitioner with mast cell disorder, urticarial vasculitis, disorder of the autonomic nervous system, flushing and headache. *Id.* at 13. Dr. Bernstein's diagnoses for petitioner of mast cell disorder and chronic urticaria from January 2020 through May 2020 did not change. *See generally* Pet. Ex. 37. He did opine that petitioner's "disorder of autonomic nervous system" may be a "sympathomimetic syndrome" and she could benefit from a low dose of Adderall. *Id.* at 9.

Throughout 2020 petitioner was treated for a variety of different conditions, including allergic rhinitis, possible COVID-19 exposure, dyspareunia, abdominal pain, oral candida infection, and GERD. *See generally* Pet. Ex. 53.

On January 26, 2021, petitioner had an appointment with Dr. Bernstein who ordered serum testing for hereditary alpha tryptasemia. Pet. Ex. 52 at 6. He also recommended that she begin a calcium supplement. *Id.* at 9. At this appointment, it appeared that petitioner's chronic urticaria was well controlled as Dr. Bernstein noted "no hives." *Id.*

Five months later, he noted that petitioner was positive for hereditary alpha tryptasemia. Pet. Ex. 52 at 4. Dr. Bernstein wrote that petitioner was doing better with her diagnosis of mast cell disorder and referred her to an ophthalmologist. *Id.*

In 2021, petitioner was treated for high blood pressure, GERD, joint pain, COVID-19 infection, and fatigue. *See* Pet. Ex. 53 at 7-40.

b. Summary of Expert Opinions

1. Petitioner's Expert-Dr. Johnathan Bernstein

Dr. Bernstein, one of petitioner's treating physicians, and expert allergist and immunologist, wrote four expert reports in support of petitioner's claim. Pet. Exs. 28, 38, 49 & 111. In his first report, Dr. Bernstein wrote that the diagnosis of MCAS is appropriate for petitioner based on her elevated tryptase level, symptoms that involve multiple organ systems, and treatment course. Pet. Ex. 28 at 1-3. Dr. Bernstein wrote that petitioner asserted that "the onset of the hives began shortly after experiencing an anaphylactic reaction [to] the influenza vaccine. After receiving the vaccine, she developed dizziness, dry mouth, difficulty swallowing, and a rash. She was seen in the ED and treated. ….Since that time, she experiences similar episodes every 1-1.5 months and has had breathing problems ever since." Pet. Ex. 28 at 1. Later, Dr. Bernstein revised his opinion of petitioner's appropriate diagnosis, stating that her condition is "hereditary alpha tryptasemia" ("HαT"), based on genetic testing confirmation. Pet. Ex. 49 at 1.

Dr. Bernstein wrote that petitioner's diagnosis of MCAS is "based on having appropriate clinical symptoms, an elevated mast cell marker indicating constitutive release of bioactive mediators from mast cells, and response to treatment with medications that block receptors which when activation can cause allergic anaphylactic symptoms similar to what [petitioner] is experiencing." Pet. Ex. 28 at 2. He wrote that "mast cell activation symptoms can involve essentially any organ system and symptoms of anaphylaxis can range from mild to severe." *Id.* Dr. Bernstein stated that petitioner's symptoms, including flushing, gastrointestinal symptoms, and joint pain, could be part of her MCAS. *Id.* at 2. Dr. Bernstein explained that patients with HαT have clinical manifestations including, "connective tissue abnormalities, symptoms suggestive of autonomic dysfunction, as such orthostatic hypotension, palpitations, tachycardia, presyncope and syncope, and constitutional symptoms such as chronic pain and fatigue." Pet. Ex. 49 at 1. He opined that petitioner's reaction to the flu vaccine "most likely occurred due to her heightened reactivity to drugs and vaccines secondary to this mast cell tryptase gene mutation of TPSAB1." *Id.* Dr. Bernstein also observed that HαT "can be overlooked in patients with autonomic dysfunction symptoms such as [petitioner]." *Id.*

An article by Lyons, Dr. Bernstein referenced in his third report, explains that patients with HαT "have elevated basal serum tryptase," and many present with multisystem complaints, including systemic immediate hypersensitivity reactions, cutaneous flushing and pruritic, functional gastrointestinal diseases, connective tissue abnormalities, and symptoms suggestive of autonomic dysfunction." Pet. Ex. 51.[12] Lyons acknowledged that that it was unknown how increased TPSAB1 copy leads to increased basal serum tryptase and the clinical features associated with HαT, "it appears that mast cells and basophils over-express and secrete pro-trypase(s) in excess when increased alpha-encoding TPSAB1 are present." *Id.* at 3. The most commonly reported clinical symptoms associated with HαT are functional gastrointestinal

[12] Lyons, J., *Hereditary Alpha Tryptasemia: Genotyping and Associated Clinical Features,* 38(3) Immunol. Allergy Clin. North Am. 483-495 (2018). [Pet. Ex. 51].

complaints. *Id.* at 6. Lyons summarized several studies of HαT patients and also observed that half of HαT patients report recurrent cutaneous symptoms such as flushing and pruritus and in a study of patients with chronic urticaria with systemic symptoms during disease flares also had high levels of basal serum tryptase. *Id.* at 6-7. Lyons also indicated that individuals with HαT have systemic reactions consistent with IgE-mediated immediate hypersensitivity reactions to stinging insects. *Id.* at 6.

The article by Weiler et al. explains that those with HαT may not always have with MCAS, but the genetic defect increases the activatability of mast cells, "making [HαT] an inherited risk factor for MCAS." Pet. Ex. 30 at 2.[13] The increased TPSAB1 gene copy numbers increase the activatability of mast cells which can result in clinical features including dysautonomia, flushing, irritable bowel syndrome, disorders affecting the skin, or the cardiovascular and respiratory systems. Pet. Ex. 30 at 4. Reported triggers of mast cells are hot water, drugs, stress, exercise, hormonal fluctuations, infection or physical stimuli, such as pressure or friction. *Id.* at 3. Weiler stated an increased basal serum tryptase level "puts a patient at increased risk for a variety of clinical problems, such as anaphylaxis, food induced allergic reactions in children, and adverse reactions to drugs, [and] insect stings." *Id.* at 4.

To explain how the flu vaccine caused petitioner's condition or at least aggravated petitioner's symptoms, Dr. Bernstein stated that "the occurrence and severity of [petitioner's] severe reaction to the flu vaccine occurred and was magnified due to her underlying hereditary alpha-tryptasemia condition." Pet. Ex. 49 at 1. He stated that there was an immediate reaction to the flu vaccine petitioner received on October 27, 2015, resulting in "immediate symptoms consisting of perioral numbness and dry mouth which progressed over a few hours to a rash, hives, dyspnea, and throat swelling." Pet. Ex. 111 at 2. Because of this immediate reaction, it caused her to seek medical attention "over 160 times for a spectrum of health issues between 2015 and 2021." *Id.*

Dr. Bernstein wrote, "There have been several case reports of reactions to vaccinations reported in patients with mast cell disease resulting in mast cell activation." Pet. Ex. 38 at 1. Bankova et al. reported on a five-month-old boy that developed a raised pruritic rash with episodic blisters twelve hours after receiving his four-month-old vaccinations, including the *Haemophilus influenzae*, protein-conjugated pneumococcal vaccine, poliomyelitis vaccine, diphtheria, pertussis and tetanus toxoid, and rotavirus vaccines. Pet. Ex. 40 at 2.[14] The authors wrote, "Immunologic stimuli can also cause mast cell degranulation through activation via Toll-like receptors," and indicated the infections, along with trauma (including surgery), can trigger mast cell activation. *Id.*

Referring to an article by Parente et al., which examined "the prevalence of vaccine-induced reactions due to mast cell activation in children with mastocytosis," Dr. Bernstein wrote

[13] Weiler, C. et al., *AAAAI Mast Cell Disorders Committee Work Group Report: Mast Cell Activation Syndrome ("MCAS") Diagnosis and Management,* J Allergy Clin. Immunol. 883-896 (2019). [Pet. Ex. 30].

[14] Bankova, L. et al., *Generalized Bullous Eruption after Routine Vaccination in a Child with Diffuse Cutaneous Mastocytosis,* J Allergy Clin Immunol: In Practice 94-96 (2013). [Pet. Ex. 40].

that the study found that children with diagnosed mastocytosis had rates of reactions to vaccinations greater than that reported in the general population. Pet. Ex. 38 at 2; Pet. Ex. 41.[15] Parente observed that four out of 72 children who had been diagnosed with mastocytosis had an adverse reaction after the first dose of a vaccine within 1 to 12 hours vaccination. Pet. Ex. 41 at 5. Two reactions included diffuse urticaria that developed 1 to 4 hours post-vaccination, and two patients developed bullous skin eruption 6 to 12 hours post-vaccination. *Id.* "All reactions were considered mild and were treated with oral antihistamines" and none of the patients required hospitalization. *Id.* Additionally, Parente observed that 40 patients diagnosed mastocytosis did not have skin lesions until months or years after vaccination and wrote, "In none of these patients was there a close temporal association between vaccination and the onset of mastocytosis or development of skin lesions at the site of injection. This observation does not support a causal relationship between vaccination and development of mastocytosis." *Id.* at 7.

With respect to how the flu vaccine could cause mast cell activation syndrome, Dr. Bernstein referenced numerous articles that discussed a relationship between influenza A and mast cell activation in both humans and mouse studies. Pet. Ex. 38 at 2. One of the articles by Liu et al., found that influenza A virus infection can "induce mast cell apoptosis." Pet. Ex. 34.[16] The authors found that the influenza A, through the mitochondria-mediated intrinsic pathway, can cause mast cell apoptosis, which allows the virus to replicate faster. *Id.* at 6-7. The Graham et al. article also examined the role of mast cells during influenza infections and stated that emerging data suggests "a link between mast cell recruitment and activation with lung immunopathology" during an influenza A infection. Pet. Ex. 31 at 5.[17] The authors wrote that the mast cell recruitment to the lungs during an influenza infection correlates with clinical symptoms of influenza and lung damage. *Id.* Importantly, Graham explains that mast cells have a wide range of receptors, and the "engagement of these receptors results in mast cell activation leading to immediate degranulation, the *de novo* synthesis of eicosanoids within minutes of activation, and the *de novo* synthesis of numerous cytokines, chemokines, and growth factors within hours of activation." *Id.* at 2. Summarizing the different phases of mast cell activation, Graham states:

> …through the release of numerous chemotactic factors and vasodilators, mast cells are optimized for the rapid initiation and propagation of an acute inflammatory response through degranulation, production of bioactive lipids, and secretion of cytokines and chemokines. The resulting leukocyte and lymphocyte infiltrate can help to maintain inflammatory state if the infection persists.

Id. at 2.

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[15] Parente, R. et al., *Evaluation of Vaccination Safety in Children with Mastocytosis,* Ped. Allergy and Immunol., doi: 10.1111/pai.12647 (2016). [Pet. Ex. 41].

[16] Liu, B. et al., *Apoptosis and Pro-Inflammatory Cytokine Response of Mast Cells Induced by Influenza A Viruses,* 9(6) PLoS e100109. doi:10.1371/journal.pone.0100109 (2014). [Pet. Ex. 34].

[17] Graham, A. et al., *Mast Cells and Influenza A Virus: Association with Allergic Responses and Beyond,* 6 Frontiers in Immunol. http://dx.doi.org/10.3389/fimmu.2015.00238 (2018). [Pet. Ex. 31].

In his final report, Dr. Bernstein referenced several articles that discuss immediate hypersensitivity reactions to vaccines, including the flu vaccine. Pet. Ex. 111 at 2. The McNeil et al. article examined different types of hypersensitivity reactions to different vaccines, stated "vaccine-associated hypersensitivity reactions are not infrequent," and that "serious anaphylactic or cutaneous adverse reactions do occur but are extremely rare." Pet. Ex. 116.[18] The article endorses urticaria and anaphylaxis as occurring after vaccination and states that the urticaria usually resolves "generally within 24-hours." *Id.* at 3. Additionally, McNeil states that "delayed-type reactions occur commonly within hours or days after exposure, although symptoms onset can be delayed up to 2 to 3 weeks," with the most common delayed-type reaction being a rash, but delayed reactions are typically self-limiting. *Id.* at 3.

Dr. Bernstein stated that "evidence in the literature supports vaccines causing mast cell activation resulting in allergic reactions similar to what was experienced by [petitioner]," and that her symptoms were temporally associated with the October 27, 2015 flu vaccine and progressed until her eventual diagnosis of HαT. Pet. Ex. 111 at 3. He concluded, "the initial influenza vaccination triggered her subclinical HαT to become more clinically active resulting in significant morbidity." *Id.*

2. Petitioner's Expert-Dr. Omid Akbari

Petitioner submitted to reports from immunologist, Dr. Omid Akbari to support her claim that the flu vaccination caused her to develop MCAS. Pet. Exs. 54, 86. In his first report, Dr. Akbari opined that "had it not been for the flu vaccination, [petitioner] would not have developed symptoms associated with MCAS." Pet. Ex. 54 at 11. Dr. Akbari stated that "the timing between receipt of the vaccine and development of symptoms is consistent with what is known about the timing of MCAS resulting from vaccinations." Pet. Ex. 54 at 12. He wrote:

> There are two sets of hypersensitivity as a result of activation in MCAS. The immediate hypersensitivity occurs within [a] few minutes after activation of mast cells with vaccines, particularly vaccines that are able to activate inflammasome pathways such as influenza vaccine. The second reaction may occur weeks later as mast cells start to release chemokines, cytokines, and proteases that often activate other immune cells and can also directly cause pathologies and symptoms such as vomiting, nausea, diarrhea, gastritis, and esophagitis and abdominal pain.

Id.

In his first report, Dr. Akbari explained that mast cells are found "near blood vessels or nerves" and are in mucosal or endothelial surfaces. Pet. Ex. 54 at 4. He stated that mast cells respond to allergic inflammation and there is a correlation between mast cell density in the tissue and severity of allergic symptoms. Dr. Akbari referenced an article by Akin et al., which described the role of mast cells and mast cell activation syndrome, to provide additional details

[18] McNeil, M. et al., *Vaccine-Associated Hypersensitivity*, 141(2) J. Allergy Clin. Immunol. 463-472 (2019). [Pet. Ex. 116].

about mast cells. *Id.* at 8; Pet. Ex. 87.[19] Akin explains that mast cells can be activated by IgE-dependent and IgE-independent mechanisms, but both result in the following: 1) degranulation with resulting release of preformed mediators stored in granules including histamine, heparin, proteases, and cytokines such as TNF-α, 2) de novo synthesis of arachidonic acid metabolites from membrane lipids, and 3) synthesis and secretion of cytokines and chemokines. Pet. Ex. 87 at 3. Dr. Akbari noted that petitioner's lack of response to Xolair (anti-IgE medication) suggests that her mast cell activation syndrome was activated with an IgE-independent mechanism. Pet. Ex. 54 at 5, n.5.

Akin explains that non-IgE mediated mechanisms for mast cell activation include IgG, complement, microbial components, drugs, hormones, physical and emotional stimuli, and cytokines. Pet. Ex. 87 at 4. Akin provides:

> These mechanisms of mast cell activation are observed in non-allergic inflammatory disorders, including chronic autoimmune urticaria. IFN-γ specifically can induce human mast cells to upregulate high affinity IgG-receptors, cross linking of which can cause mast-cell degranulation. This mechanism of mast cell activation may be operational in IFN-γ rich autoimmune disease states such as psoriasis and in inflammatory bowel disease.

Id.

In explaining how the flu vaccine could result in MCAS, Dr. Akbari initially provided a discussion about how the adjuvant in the vaccine "facilitates the induction of immune responses mainly by triggering pathways such as inflammasome." Pet. Ex. 54 at 8. He provided a detailed explanation of how alum achieves inflammatory effects, leading to inflammasome complexes which leads to increased caspase-1 activity, turning inactive cytokines in the IL-1 family (including IL-1α and IL-1β) to their active forms. *Id.* at 7-8. He wrote, "Since these cytokines are potent stimulators of adaptive responses, the inflammasome is a primary target of these toxins or adjuvant." *Id.* at 8. However, respondent's expert, Dr. Soman N. Abraham correctly observed that the flu vaccine petitioner received did not contain an adjuvant. Resp. Ex. E at 2.

Responding to this observation, Dr. Akbari modified his opinion by stating that the flu vaccine, even in the absence of an adjuvant, still activates inflammasome, which leads to the secretion of pro-inflammatory cytokines after a flu vaccination. Pet. Ex. 86 at 3-4. Dr. Akbari refers to an article by Crooke et al., which measured inflammasome activity in response to the flu vaccine in different age populations, to support his opinion that the flu vaccine without an adjuvant can activate the inflammasome pathway. Crooke et al. examined inflammasome activity in older adults compared to a younger cohort to determine if the lack of inflammasome response was responsible for decreased adaptive immunity. Resp. Ex. E, Tab 1.[20] The authors

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[19] Akin, C. et al. *Mast Cell Activation Syndrome: Proposed Diagnostic Criteria,* 126(6) J. Allergy Clin. Immunol., 1099-1104 (2010). [Pet. Ex. 87].

[20] Crooke, S. et al., *Inflammasome Activity in Response to Influenza Vaccination Is Maintained in Monocyte-Deprived Peripheral Blood Macrophages in Older Adults,* 2 Frontiers in Aging, doi: 10.3389/fragi.2021.719103 (2012). [Resp. Ex. E, Tab 1].

explained that the "influenza virus M2 protein or the PB1-F2 polymerase stimulate activation of the NLRP3 inflammasome complex and activation of the inflammasome complex leads to increased caspase-1 activity, the processing of inflammatory cytokines into their bioactive forms, and ultimate release of inflammatory mediators." *Id.* at 1. Dr. Akbari also referenced the Hartenian and Broz article, which summarizes the Yang et al. article, and explains that viral antigens bind to the NLRP1inflammasome complex, which then activates and releases cytokines. Pet. Ex. 86 at 2; Pet. Ex. 94.[21] Dr. Akbari wrote that Yang and Hartenian demonstrate that the flu vaccine triggers inflammasome, which is critical to the response to the vaccine. Pet. Ex. 86 at 4.

Dr. Akbari then attempted to link the mast cell activation to the secretion of the cytokines. Pet. Ex. 86 at 5. He referenced the Kayamuro et al. article, which explores using cytokines as adjuvants in the mucosal vaccines against influenza viruses, to demonstrate that cytokines such as IL-18 and IL-33, can activate mast cells, potentially leading to an increase in antigen specific mucosal immune response induced by the IL-1 cytokine family. Pet. Ex. 95 at 1, 6.[22] However, petitioner's vaccine was not a nasal vaccine, but instead one that was injected into her right deltoid. *See* Pet. Ex. 1.

Then Dr. Akbari discussed the role of regulatory T cells in maintaining immune homeostasis and suppress self-reactive cells. Pet. Ex. 86 at 8. He opined that the T-regulatory cells in the skin and mucosal tissue are incapable of controlling inflammation, and in "individuals such as [petitioner] with high activity of mast cells and inflammatory pre-condition, after vaccination, pathogenic T-effector cells are able to induce mast cell mediated activation, and this is partially due to impaired [T-regulatory cells]." *Id.* at 10. Referencing an article by Li et al, and co-authored by prominent senior immunologist, Dr. Mark Davis, Dr. Abkari wrote, "[T]he authors showed that these CD-8 [T-regulatory] are induced as part of the response during an autoimmune reaction or exposure to pathogens and may act as a negative feedback mechanism to specifically suppress the self-reactive or otherwise pathogenic cells without affecting the immune response against pathogens. This subset of CD-8 Tregs appear to play an important role in maintaining peripheral tolerance, which is distinct from and likely complementary to that of CD-4 T-regulatory cells." Pet'r Ex. 86 at 9; *see also* Pet'r Ex. 100.[23] Dr. Akbari explained that regulatory T-cells can inhibit the induction of autoimmunity after exposure to an antigen and that in experimental mice that were deficient in CD-8 T-cells, when infected with viruses "eventually developed symptoms of autoimmune disease." Pet'r Ex. 86 at 9. Li hypothesized, after showing that KIR+CD8+T-cells were increased in the blood and in the tissues of patients with autoimmune disease, that CD8+ regulatory T-cells are meant to control autoreactive T cells that may be activated during an infection and cross-reacting with a foreign antigen. *Id.* at 5.

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[21] Hartenian, E. & Broz, P., *Viral Protein Activates the NLRP1 Inflammasome,* 23 Nature Immunol. 822-23 (2022). [Pet. Ex. 94].

[22] Kayamuro, H. et al., *Interleukin-1 Family Cytokines as Mucosal Vaccine Adjuvants for Induction of Protective Immunity Against Influenza Virus,* 84 J of Virol. 12703-12717 (2010). [Pet. Ex. 95].

[23] Li, J. et al., *KIR-CD-8 T-cells Suppress Pathogenic T-cells and are Active in Autoimmune Diseases and COVID-19,* Science, doi:10.1126/scienceabi9591 (2022). [Pet. Ex. 100].

After presenting this general information regarding the regulatory system and the role of T-regulatory cells, Dr. Akbari stated that, "The crosstalk between T-regulatory cells and mast cells is important as T-regulatory cells are capable of suppressing inflammatory responses and inhibit mast cell degranulation. Loss of this interaction may contribute to the severity of mast cell responses including urticaria." *Id.* Dr. Akbari opined that in a patient with "high activity of mast cells and inflammatory precondition, after vaccination, pathogenic T effector cells (including B and T cells) are able to induce mast cell mediated activation, partially due to the impaired T-regulatory cells. *Id.*

Dr. Akbari also addressed the immediate response to the flu vaccine and how it can cause early mast cell activation and then a later reaction. He wrote that "the primary early-phase mediator, histamine, peaks in tears between 15 to 20 minutes after antigen exposure and tryptase peaks at about the same time, making it a specific marker for early-phase histamine release from mast cells." Pet. Ex. 86 at 12. Then, histamine release undergoes a second peak with the late-phase release, but tryptase does not increase during late-phase reactions, making it possible for a patient with mast cell activation to have both early and late hypersensitivity symptoms. *Id.* He referenced an article by Tomimori et al., which explored mast cell skin reactions to intradermal injections of chymase, an enzyme inside of mast cells, found that the first skin reaction "was transient and peaked 1 hour after the chymase injection, whereas the second reaction reached a maximal level at 6 hours and lasted for at least 24 hours." Pet. Ex. 106 at 2.[24] Dr. Akbari asserted that it is possible for the flu vaccine to trigger an immediate hypersensitivity reaction and a later, second one that occurs weeks later "as mast cells start to release chemokines, cytokines, and proteases that often activate other immune cells and can also directly cause pathologies and symptoms such as vomiting, nausea, diarrhea, gastritis, and esophagitis, and abdominal pain." Pet. Ex. 86 at 13.

While not fully explaining how the flu vaccine could trigger delayed reactions by mast cells, Dr. Akbari simply reiterated Dr. Bernstein's supplemental report that noted petitioner's immediate reaction and then later medical appointments for a "spectrum of health issues," that came after the flu vaccine at issue in this case. Pet. Ex. 86 at 13.

Dr. Akbari concluded that, "It is now acceptable in the field that vaccines and immunization can exacerbate symptoms associated with mast cell mediator release including urticaria, pruritus, and diarrhea. Therefore, it is my opinion that, in this case, the scientific research supports the assertion that stimulation of the immune system following vaccination, is a credible medical theory linking the flu vaccination with the development of urticaria and associated inflammatory symptoms in [petitioner]." Pet. Ex. 86 at 13-14.

3. Respondent's Expert- Dr. Soman Abraham

Respondent filed two expert reports from Dr. Abraham, who is a pathologist and immunologist. Respt. Ex. A, E. Dr. Abraham agreed with Dr. Bernstein's diagnosis of Mast

[24] Tomimori, Y. et al., *Role of Mast Cell Chymase in Allergen-Induced Biphasic Skin Reaction,* 64 Biochemical Pharm. 1187-1193 (2002). [Pet. Ex. 106].

Cell Activation Syndrome (MCAS) for petitioner and noted that Dr. Bernstein is an "accomplished allergy specialist who is knowledgeable about the diagnosis of MCAS." Resp. Ex. A at 5.

Consistent with Dr. Bernstein's description of MCAS, Dr. Abraham wrote, "MCAS is a condition in which the patient experiences repeated episodes consistent with the symptoms of anaphylaxis—allergic symptoms as with vomiting, diarrhea, abdominal cramping, urticaria, flushing, nausea, loss of consciousness, accelerated heart rate, wheezing, itching, and swelling underneath the skin, and nasal stuffiness." Respt. Ex. A at 5. He noted that MCAS is associated with chronic inflammation with or without allergic-type symptoms, and can develop over time with "flare-ups." *Id.* Further, he described a subset of "clonal MC disease" that is associated with hereditary alpha-tryptasemia, where patients have extra inherited copies of the gene TPSAB-1 that produces extra α-tryptase and leads to high tryptase in the peripheral blood. *Id.*

Dr. Abraham described both IgE-dependent mast cell reactions, and also the IgE-independent activation of mast cells in response to a variety of different triggers, including bacteria, drugs, foods, fungi, viruses and certain neuropeptides. Resp. Ex. A at 6. The articles by Redegeld et al. and Theoharides et al., referenced by Dr. Abraham, explain that aside from the IgE-mediated mast cell activation, mast cells have numerous receptors that are able to respond to different pathogens and adjust their response according to the stimulus. *See* Resp. Ex. A, Tab 22 at 18[25]; Resp. Ex. A, Tab 23 at 3-4[26]. Further, he wrote that not all stimulation of mast cells leads to degranulation, but mast cells can secrete other mediators, including TNF and IL-17, which can then lead to the recruitment of other immune cells. Resp. Ex. A, Tab 23 at 4. Dr. Abrahams opined that given the vast repertoire of receptors on mast cells and their widespread location through the body, it is difficult to identify specific triggers that result in mast cell activation and aberrant responses. Resp. Ex. A at 6.

Dr. Abraham explained that there are two types of genetic conditions that are associated with MCAS, one being patients who have a somatic mutation in the C-kit gene (most commonly in the D816V mutation) and the other is the genetic condition "hereditary alpha-tryptasemia." Resp' Ex. A at 7. Dr. Abraham observed that Dr. Bernstein had diagnosed petitioner with the genetic disorder of HαT, a subtype of MCAS. *Id.* at 5.

Turning to whether the flu vaccination could cause or exacerbate MCAS, Dr. Abraham wrote that the literature Dr. Bernstein relied upon was irrelevant because the articles are describing reactions to patients who were already diagnosed with MCAS and not examples of vaccinations being the cause of MCAS. Resp. Ex. A at 7. He stated, "MCAS patients periodically experience flare-ups upon exposure to a variety of known and unknown environmental stimulants, but there is, as yet, no evidence for a particular stimulant being the cause of this chronic inflammatory condition. *Id.* Dr. Abraham also argued that the literature Dr. Bernstein relied upon describes adverse reactions to vaccines other than the flu vaccine. *Id.*

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[25] Redegeld, F. et al., *Non-IgE Mediated Mast Cell Activation,* 282 Immnol. Reviews, 87-113 (2018). [Resp. Ex. A, Tab 22].

[26] Theoharides, T. et al., *Recent Advances in Our Understanding of Mast Cell Activation-or Should it be Mast Cell Mediator Disorders?,* 15(6) Expert Rev. Clin. Immunol., 639-656 (2019). [Resp. Ex. A, Tab 23].

Finally, he argues that the examples in the literature cited by Dr. Bernstein are "exclusively in patients who appear to have the clonal version of MCAS linked to a genetic defect—e.g. c-kit mutations," and the petitioner does not have the c-kit mutation. *Id.*

Dr. Abraham acknowledged that there was a temporal relationship between the flu vaccine and an allergic reaction that occurred five minutes after vaccination, however, he argued that Dr. Bernstein "has neglected to connect [petitioner's] flu vaccination with the numerous visits to the hospital she made starting over a month after the vaccination. This is an important omission as the diagnosis of MCAS is based on the clinical symptoms that emerged during those visits." Resp. Ex. A at 8.

Dr. Abraham also disagreed with Dr. Akbari's opinion that the flu vaccination was the cause of petitioner's MCAS. He observed that Dr. Akbari's first report discussed the role of alum in the vaccine and explained that the flu vaccine petitioner received did not include alum. Resp. Ex. A at 10. Responding to Dr. Akbari's second report, in which he discussed how the flu vaccine can induce inflammasome, causing inflammation and urticaria, Dr. Abraham conceded that the flu vaccine can cause limited swelling, heat, and soreness at a vaccination injection site, but argued that this explanation does not explain the systemic issues petitioner later experienced. Resp. Ex. E at 3.

Dr. Abrahams also asserted that Dr. Akbari's second report focuses largely on unrelated topics to MCAS. Resp. Ex. E at 5. Dr. Abraham stated that the section of Dr. Akbari's report focused on Regulatory T-cells is relatively disconnected to petitioner's condition of MCAS and much of the literature Dr. Akbari references are related to demyelinating diseases. He stated that that T-regulatory cells do not have any bearing on MCAS. *Id.* at 4-5.

Ultimately, Dr. Abraham concluded that individuals that are genetically susceptible to developing MCAS, like petitioner, will experience flare-ups in MCAS symptoms when exposed to different environmental triggers. Resp. Ex. A at 12. He opined that the flu vaccine is not a causative agent of MCAS, but instead an environmental trigger, and because the petitioner was genetically prone to MCAS, she developed a flare-up in the form of an allergic reaction immediately after vaccination. However, he argued that her later hospitalizations and treatments were unrelated to the flu vaccine or that initial reaction. *Id.*

4. Respondent's Expert—Dr. Chester Oddis

Respondent submitted one expert report from Dr. Chester Oddis, an immunologist and rheumatologist. Resp. Ex. C. Dr. Oddis did not dispute petitioner's diagnosis of MCAS. *Id.* at 5. Instead, he argued that petitioner's symptoms associated with MCAS were "well documented in her medical records months and years prior to being vaccinated in October 2015." *Id.*

He wrote, "I did not see that she reported urticaria prior to vaccination, but she certainly was evaluated for syncope and near-syncope, flushing, chest pain, nausea, vomiting, abdominal pain, headaches, sinusitis, mayalgias and arthralgias l on multiple occasions during the years prior to October 2015." Resp. Ex. C at 5. Dr. Oddis also observed that petitioner had "some

degree of elevation of inflammatory markers, ESR and CRP over two years prior to receiving the flu vaccine compared to the results of these inflammatory markers noted after vaccination." *Id.*

Making a similar argument as Dr. Abraham's, Dr. Oddis stated that some of the literature Dr. Bernstein referenced were related to patients with a known diagnosis of MCAS, "which is quite different than asserting that vaccination caused MCAS." Resp. Ex. C at 6. He also disagreed with Dr. Akbari's opinion that the flu vaccine caused petitioner's MCAS, and wrote "his opinion that [petitioner] would not have developed her constellation of symptoms had she not received the flu vaccine is wholly conclusory." *Id.* Dr. Oddis agreed that petitioner's diagnosis was MCAS, but opined that it appeared to be a long-standing condition, with relevant symptoms occurring both prior to the flu vaccine and afterwards. He concluded that the flu vaccine did not cause petitioner's MCAS. *Id.*

IV. Analysis

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 & Hum. Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 543, 549 (Fed. Cir. 1994). In this case, petitioner has not presented a sound and reliable theory by preponderant evidence to demonstrate how the flu vaccine can cause mast cell activation syndrome.

All the experts in this case agree that petitioner's appropriate diagnosis is hereditary alpha-tryptasemia ("HαT"), which is a possible subtype of mast cell activation syndrome ("MCAS"). Resp. Ex. E at 2; Pet. Ex. 49 at 2. Additionally, the experts agree that petitioner experienced some type of anaphylactic reaction that began five minutes after she received the flu vaccine on October 27, 2015. Pet. Exs. 49; Resp. Ex. A at 8. However, the experts disagreed that the flu vaccine could cause long running and intermittent symptoms of MCAS, or that it did in this case.

To show vaccine causation, petitioner must put forth a sound and reliable theory for how the vaccine could cause her underlying condition or significantly aggravate that condition. In this case, petitioner has failed to provide a sound and reliable theory to explain how the flu vaccine can cause MCAS or significantly aggravate an underlying HαT beyond her initial reaction on October 27, 2015. This failure is particularly pronounced in light of her ultimate diagnosis of hereditary alpha tryptasemia which appears to well explain the long history both before and after vaccination of her array of medical problems.

Hereditary alpha tryptasemia ("HαT") is an autosomal dominant genetic trait caused by increased copies of TPSAB1 encoding α-tryptase. Resp. Ex. A, Tab 12 at 2; *see also* Pet. Ex. 51. HαT is characterized by an elevated baseline serum tryptase level and is present in approximately 5% of Western populations. Resp. Ex. A, Tab 10 at 1. Commonly reported clinical symptoms of patients with HαT are functional gastrointestinal complaints, along with

recurrent cutaneous symptoms, including flushing and pruritus, induration, and angioedema. Pet. Ex. 51 at 6. Other clinical manifestations associated with the hereditary alpha-tryptasemia includes connective tissue abnormalities; autonomic dysfunction such as orthostatic hypotension, palpitations, tachycardia, presyncope and syncope; and food intolerances. *Id.* at 7. Lyons explained that some symptoms of individuals with HαT were spontaneous, while other symptoms are suggestive of mast cell mediator release, few patients have identifiable evidence of chronic mast cell mediator release. *Id.* at 6; *see also* Resp. Ex. T, Tab 12 at 2-3. "Systemic reactions consistent with IgE-mediated immediate hypersensitivity to stinging insects have been reported in approximately 20% of patients with HαT," and the prevalence is 3-4 fold that of what has been reported in similar populations. *Id.*

There is an overlap between patients with mast cell activation disorders and what? HαT?, According to Vazquez et al., "two studies have demonstrated HαT to be a major modifier of clonal and non-clonal mast-cell associated disorders, including systemic mastocytosis, idiopathic anaphylaxis, and venom allergy." Pet. Ex. 119 at 1.[27] Individuals with HαT have elevated basal serum tryptase and when mast cells degranulate, mature tryptases are released with other mast cell mediators and may contribute to symptoms associated with HαT or MCAS. Pet. Ex. 51 at 1-4.

Dr. Bernstein opined that the flu vaccine petitioner received on October 27, 2015 "triggered her subclinical hereditary alpha tryptasemia to become more clinically active." Pet. Ex. 111 at 3. Aside from the temporal association between petitioner's initial reaction to the flu vaccine, Dr. Bernstein and Dr. Akbari do little to explain how the flu vaccine and petitioner's initial reaction then caused other symptoms commonly associated with HαT that appeared months later.

The medical literature acknowledges that patients with mastocytosis "in general have an increased incidence of adverse reactions to exogenous agents," and that vaccines can induce generalized flushing, pruritus, urticaria, bullous lesions, or gastrointestinal symptoms in individuals with mastocytosis. Resp. Ex. A, Tab 27 at 9. Additionally, McNeil provides that nearly all vaccines have the potential to trigger anaphylaxis or an immediate hypersensitivity reaction. Pet. Ex. 116 at 1, 8. However, the medical literature, nor the expert opinions, explain how an initial, immediate reaction, could result in symptoms that develop months or nearly a year later, as they did in petitioner. The Bankova and Parente articles Dr. Bernstein relies upon to support his opinion that the flu vaccine caused petitioner's initial reaction, only demonstrate immediate adverse reactions to vaccines in patients who had been diagnosed with mastocytosis and these articles do not support a causal connection between vaccination and onset of mastocytosis. Further, the McNeil article suggests there can be some type of delayed hypersensitivity reaction to a vaccine, but that delayed onset typically occurs within hours or days, and in this case, petitioner did have an immediate hypersensitivity reaction. *See* Pet. Ex. 116 at 3. None of these articles actually suggests that an immediate reaction to a vaccine in a patient with MCAS continued past a short-time period. But the course of intermittent flares of symptoms, the first occurring 45 days post- vaccination, and other weeks and months apart

[27] Vazquez, M. et al., *Hereditary Alpha-Tryptasemia Modifies Clinical Phenotypes Among Individuals with Congenital Hypermobility Disorders,* 3 Hum. Genetics and Genomic Advances, 1-3 (2022). [Pet. Ex. 119].

including the onset of urticaria nearly a year later are symptoms consistent with an HαT genetic disorder, and are unrelated to the flu vaccine.

Parente, examined adverse vaccine reactions in 72 pediatric patients diagnosed with cutaneous mastocytosis, found that only four children had an adverse reaction to the first Hexavalent vaccine (DTaP/IPV/HepB/IPV), which began 6 to 12 hours after vaccination and resolved with oral antihistamine treatment. Pet. Ex. 41 at 5. The authors explained that the reactions occurred in children with pre-existing mastocytosis skin lesions, and that while there is no conclusive evidence that the reactions were due to mast cell activation induced by vaccine components, "the close time relationship between the onset of clinical manifestations and vaccine administration makes the procedure a likely trigger of the reactions." *Id.* at 6. Parente also observed that the presentation of skin lesions leading to the diagnosis of mastocytosis appeared "at variable times ranging between 4 and 60 months after the initiation of the vaccination schedule." *Id.* The authors concluded:

> In 40 patients, the typical skin lesions of mastocytosis appeared months or years after the vaccination program had been initiated. In none of these patients was there a close temporal association between vaccination and onset of mastocytosis or development of skin lesions at the site of injection. This observation does not support a causal relationship between vaccination and the development of mastocytosis.

Id. at 7.

Aside from the case reports described above, in which a vaccine, although not the flu vaccine, likely triggered an isolated event in patients with mastocytosis, nothing in the medical literature explains how an isolated anaphylactic response can result in the progressive, clinical course seen in petitioner's case with the next flare occurring forty-five days later. Instead, the medical literature recognizes that mast cell activation can be activated by other stimuli including drugs, hormones, physical and emotional stimuli, or viral pathogens. Pet. Ex. 87 at 4-5.

Dr. Akbari's opinion also does little to close the gap between petitioner's initial reaction and her later developed symptoms, including urticaria and gastrointestinal issues. Dr. Akbari's first report explored the role of alum in stimulating mast cells, however, respondent's experts correctly observed that the vaccine petitioner received, did not contain the alum adjuvant, rendering this portion of his opinion irrelevant. Dr. Akbari's second report also failed to provide a reliable theory to explain how the flu vaccine could cause progressive mast cell activation, and he failed to consider that the onset of petitioner's chronic urticaria came one year after vaccination. *See* Pet. Ex. 86 at 5. Attempting to bridge the temporal gap between petitioner's initial reaction that occurred five minutes post-vaccination to later events, including her December 11, 2015 gastrointestinal issue of right flank pain and vomiting, Dr. Akbari references the Tomimori article, but the researchers found that late phase mast cell reaction after exposure to certain proteins remained elevated for approximately 24-hours, but then decreased. Pet. Ex. 106 at 1-2. However, this article does not explain how an initial reaction may would cause another reaction or mast cell activation forty-four days later or even a year later.

Finally, none of petitioner's experts provided a sound and reliable theory to explain how the flu vaccine could significantly aggravate recurrent or progressive symptoms in an individual with HαT. Instead, the literature suggests that patients with HαT have multisystem symptoms which have been associated with food allergies, insect stings/bites or spontaneously appear, and one trigger has not been identified. *See* Pet. Ex. 51 at 6. None of the articles filed implicate any vaccines as triggers for unmasking or making clinical symptoms worse in patients with HαT. Thus, petitioner's experts have failed to provide a sound and reliable theory for how the flu vaccine can cause a worsening of symptoms in a patient with HαT and MCAS or cause MCAS.

b. *Althen* prongs two and three

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by the facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326.

The third *Althen* prong requires petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *De Bazan v. Sec'y of Health & Hum. Servs.,* 539 F.3d 1347, 1352 (Fed. Cir. 2008); *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532,542 (2011), *recons. den'd after remand,* 105 Fed. Cl. 353 (2012); *aff'd mem.,* 503 Fed. Appx. No. 11-355V, 2013 WL 3214877, at * 26 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd.*, (Fed. Cl. 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

In this case, *Althen* prongs two and three are connected. It is conceivable that the petitioner's initial anaphylactic event, which began approximately five minutes post-vaccination was triggered by the flu vaccine she received on October 27, 2015. Parente describes immediate cutaneous reactions to certain vaccines in pediatric patients that have been diagnosed with mastocytosis. Pet. Ex. 41 at 5. Additionally, McNeil describes allergic reactions to vaccines that typically occur within 24 hours of vaccination, including after administration of the flu vaccine, that can result in generalized urticaria, wheezing, swelling of the mouth, tongue, and throat, vomiting, and hypotension. Pet. Ex. 116 at 3. McNeil explains that these events are often self-limiting and resolve within 24-hours. *Id.* at 3. Therefore, petitioner's immediate reaction to the flu vaccine was likely a result of her underlying HαT, but not the later symptoms, which are more readily explained by her HαT and MCAS that were present prior to vaccination and continued afterward consistent with course of HαT as described in the medical literature.

The medical records demonstrate that petitioner was experiencing gastrointestinal issues, dyspnea and flushing, and vasovagal episodes, consistent with both HαT and MCAS, prior to the vaccination and then continued afterwards. Two and a half years prior to the vaccination at issue, on June 20, 2013, petitioner had an appointment with her primary care physician, Dr. Morton, after a trip to the emergency room for a vasovagal episode that occurred 45 minutes after she ate. Pet. Ex. 11 at 412. Petitioner explained she had a headache, nausea, vomiting, numbness and tingling and these symptoms were occurring intermittently for four days. *Id.* Petitioner experienced a similar episode one month later, on July 18, 2013, where petitioner

described having elevated blood pressure, and four episodes of flushing with associated dyspnea. *Id.* at 387. At this appointment, petitioner also endorsed having mild and intermittent diarrhea. *Id.* at 388. Petitioner was diagnosed with syncope and Dr. Morton gave her a referral to a cardiologist. *Id.* at 390. When she was evaluated by cardiologist, Dr. John Loventhal, he noted that petitioner had three episodes of chest discomfort that would come and go, lasting for about three hours in an intermittent manner. Pet. Ex. 11 at 386. He also wrote that petitioner has "active gastroesophageal reflux disease" and had "borderline thyroid disease with an enlarged thyroid." *Id.* Dr. Loventhal's impression was, "atypical chest pain of uncertain etiology; palpitations with negative Holter monitory other than sinus tachycardia; hypertension; gastroesophageal reflux disease; history of possible irritable bowel syndrome." *Id.*

Petitioner's gastrointestinal issues continued after vaccination as well. Forty-four days post-vaccination, on December 11, 2015, petitioner sought treatment for right flank pain, vomiting, and dizziness. Pet. Ex. 9 at 115. Petitioner's gastrointestinal issues continued with some regularity between December 2015 and the fall of September 2016, and at each time, petitioner presented with similar, if not the same symptoms as she had prior to the October 27, 2015 vaccination. For example, on May 4, 2016, petitioner had right lower abdominal pain with diarrhea, then on July 24, 2016, she again experienced right flank pain with associated diarrhea. *See* Pet. Ex. 9 at 58, 76. When petitioner sought treatment during another episode of gastrointestinal issues on September 1, 2016, petitioner explained that she had been experiencing these episodes since 2011, four years prior to the vaccination in October 2015 and that they had occurred multiple times. Pet. Ex. 7 at 137. Both prior to the vaccination and after vaccination, many providers opined that petitioner may have irritable bowel syndrome. *See* Pet. Ex. 7 at 142 ("Her symptoms [are] almost like irritable bowel syndrome"); Pet. Ex. 9 at 78 (differential diagnosis includes irritable bowel syndrome); Pet. Ex. 11 at 386 (noting a history of possible irritable bowel syndrome).

The gastrointestinal symptoms petitioner experienced prior to the vaccination, which continued post-vaccination are consistent with the description of gastrointestinal symptoms experienced by patients with HαT. Lyons states that "the most commonly reported clinical symptoms among individuals with HαT are functional gastrointestinal complaints," and that irritable bowel syndrome was reported in half of HαT individuals. Pet. Ex. 51 at 6. Weiler also explained that gastrointestinal symptoms of abdominal pain, diarrhea, nausea, and vomiting are frequently reported in patients with MCAS and in patients with HαT. Pet. Ex. 30 at 886.

Similarly, petitioner's urticaria is not temporally related to the flu vaccine she received on October 27, 2015 and is better explained by her underlying HαT. Importantly, petitioner's urticaria began in October 2016, nearly a year after the vaccination, and she did not have any intermittent medical appointments between the vaccination and October 2016 where petitioner described having a rash or urticaria. *See* Pet. Ex. 3 at 1 (onset of rash while on vacation in South Carolina.); Pet. Ex. 11 at 337 (petitioner reported rash starting first week of October 2016 while on vacation at the beach). Again, the medical literature supports a finding that the petitioner's urticaria was more likely related to her underlying HαT and MCAS than the flu vaccine. Urticaria is a commonly reported symptom in patients with MCAS and in patients with HαT other cutaneous symptoms, such as flushing, angioedema, and urticaria were recurrent. *See* Pet. Ex. 30 at 3; Pet. Ex. 51 at 6. Weiler and Lyons explain that the onset of the cutaneous symptoms

was spontaneous, but potential triggers included heat, alcohol, stress, drugs, hormonal fluctuations, infection, and/or physical stimuli such as pressure or friction. Pet. Ex. 30 at 3; Pet. Ex. 51 at 6. Thus, not only was the onset of petitioner's urticaria temporally remote to the October 27, 2015 flu vaccine, but there was no connection to her initial anaphylactic reaction to the later onset of her urticaria.

Despite being diagnosed with HαT and MCAS after the October 27, 2015 flu vaccine, the record preponderantly demonstrates that she had been experiencing symptoms consistent with HαT prior to the vaccination and continued to experience after the vaccination at issue. It is also unlikely that the vaccine caused a delayed hypersensitivity response resulting in multiple medical appointments after the October 27, 2015 vaccination, as the medical literature explains that individuals with HαT and MCAS may have episodic symptoms with no defined trigger. *See* Pet. Ex. 30 at 1. Aside from her initial anaphylactic event post-vaccination, which resolved relatively quickly, there is no logical sequence of cause and effect between her other medical issues, including her gastrointestinal issues or chronic urticaria. Additionally, there is no temporal association between the flu vaccination and her well documented gastrointestinal symptoms that occurred prior to vaccination and continued afterwards or her chronic urticaria which began a year after the October 27, 2015 flu vaccine. The medical literature, and her diagnosis of HαT and MCAS by Dr. Bernstein provide a more logical explanation petitioner's condition. Accordingly, the petitioner cannot preponderantly satisfy *Althen* prongs two and three.

V. Conclusion

For the reasons discussed above, after considering the evidence in the record, including the expert reports, medical literature, and petitioner's medical records, the undersigned finds that petitioner has not demonstrated by preponderant evidence that her condition was caused or exacerbated by the flu vaccine she received on October 27, 2015. Accordingly, this case is dismissed.

IT IS SO ORDERED.

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