In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-1465V

(To be published)

GERALD TEMES, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Chief Special Master Corcoran Dated: May 12, 2020 Cryoglobulinemia; Influenza Vaccine; Pneumococcal Vaccine; Vasculitis; Case Reports; Onset Timeframe

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Robert P. Coleman, III, U.S. Dep't of Justice, Washington, DC, for Respondent.

ENTITLEMENT DECISION[1]

On November 7, 2016, Gerald Temes filed a petition seeking compensation under the National Vaccine Injury Compensation Program ("Vaccine Program")[2] alleging that he experienced cryoglobulinemia,[3] a blood disorder than can lead to vasculitis, as a result of receiving

[1] This Decision shall be posted on the Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012)). **This means that the Decision will be available to anyone with access to the internet.** As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request 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). Otherwise, the whole Decision will be available to the public. *Id*.

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

[3] Cryoglobulinemia is a condition in which certain immunoglobulins (antibodies) found in the blood precipitate under cool conditions. *Dorland's Illustrated Medical Dictionary* 438, 908 (33d ed. 2020) (hereinafter *Dorland's*).

the influenza ("flu") and pneumococcal (Prevnar 13)[4] vaccines on October 19, 2015. Petition ("Pet.") (ECF No. 1) at 1. An entitlement hearing was held on September 10, 2019, in Washington, D.C., and the parties subsequently filed post-hearing briefs, completing that process in late-November of 2019.

The matter is finally ripe for resolution. After review of the record and all submissions, I deny an entitlement award in this case. As discussed in greater detail below, the record does not permit the conclusion that either vaccine—individually or in combination—*can* cause cryoglobulinemia, or that they did so in this case.

I. Factual Background

Vaccinations and Presenting Symptoms

Dr. Temes a retired thoracic surgeon, was 76 years old when he received the flu and pneumococcal vaccines on October 19, 2015. Vaccine Administration Record, filed as Ex. 8 on Feb. 2, 2017 (ECF No. 8-2); Hearing Transcript, filed Oct. 10, 2019 (ECF No. 50) ("Tr.") at 5–6, 8. At the time of his vaccination, Dr. Temes had a medical history significant for coronary artery disease, high blood pressure, high cholesterol, and mild osteoarthritis, and he had undergone a coronary artery bypass surgery in 2009. Ex. 1 at 22; Tr. at 13–15.

On October 26, 2015 (approximately one week after receiving the flu and pneumococcal vaccines), Dr. Temes was seen by Dr. Tuna Ozyurekoglu at the Kleinert Kutz & Associates Hand Care Center in Louisville, Kentucky for hand discoloration. Ex. 3 at 6. Dr. Ozyurekoglu initially expressed the view that Dr. Temes's condition was likely associated with Raynaud's phenomenon.[5] *Id.* While at the office, Petitioner's hands were warmed and normal color was restored. *Id.* at 9. That same day, Dr. Temes presented to his primary care physician, Dr. Matthew Rogers, M.D., at the Associates in Internal Medicine, where he now complained of a persistent fever that had started three days prior, as well as swelling and pain in his hands and legs. Ex. 1 at 16. A physical examination revealed cyanosis[6] in his fingers and toes. *Id.* at 20. Concerned that Dr. Temes was experiencing cryoglobulinemia, Dr. Rogers ordered Dr. Temes to undergo laboratory testing and to return for follow-up care. *Id.* at 20–21.

[4] Prevnar13 is a sterile suspension pneumococcal vaccine targeted against thirteen strains of the *Streptococcus pneumoniae* bacterium. It also contains non-toxic diphtheria protein and aluminum adjuvants. Prevnar 13 Package Insert, filed as Court Ex. 1 on May 12, 2020 (ECF No. 58) at 25–26.

[5] Raynaud's phenomenon is bilateral ischemia in the fingers or toes that causes paresthesia and pain and is usually induced by cold exposure and relieved by heat. *Dorland's* at 1430. It is usually associated with an underlying condition but can sometimes be idiopathic. *Id.*

[6] Cyanosis is a bluish discoloration of the skin caused by oxygen-depleted blood. *Dorland's* at 452.

A few days later, Dr. Temes sought care with Dr. John Huber, M.D. at the CBC Group in Louisville, Kentucky on October 30, 2015. Ex. 16 at 273. Dr. Huber noted that laboratory test results showed Petitioner possessed a slightly elevated rheumatoid factor[7] of 24 and suppressed complement levels with C3 at 75 and a C4 at undetectable levels[8], but negative cold agglutinins.[9] The result for cryoglobulins was still pending. *Id.* Dr. Temes again reported that his symptoms had developed approximately one week after receiving the flu and pneumococcal vaccines. *Id.* at 274. Dr. Huber performed a physical examination and noted that Dr. Temes's fingers and toes continued to show signs of ischemia.[10] *Id.* at 276. He concluded that Dr. Temes was likely experiencing mixed cryoglobulinemia as a result of the flu vaccine that he had received, though the pending cryoglobulin labs were needed to confirm the diagnosis. *Id.* at 277. He prescribed prednisone and discussed the possibility of immunosuppressive therapy if Dr. Temes's condition did not improve. *Id.*

On November 2, 2015, Dr. Temes saw Dr. Jeffrey Callen, M.D., a dermatologist, for follow-up care regarding his previously-treated skin fungal infection. Ex. 2 at 12. During the appointment, Dr. Temes described getting the flu shot and then subsequently developing discoloration in his hands and feet. *Id.* Dr. Callen then performed a physical evaluation, at which time he noted that Dr. Temes's fingertips remained bluish in color. *Id.* Dr. Callen proposed that Dr. Temes's symptoms were likely due to either neuropathy or Raynaud's phenomenon, but he also discussed a possible relationship between cold agglutinin problems secondary to vaccination. *Id.* Dr. Callen agreed with Dr. Huber's mixed cryoglobulinemia diagnosis, and he recommended continued treatment with prednisone. *Id.*

Dr. Temes returned for a follow-up appointment with Dr. Huber on November 5, 2015, for "[s]uspected cryoglobulinemia in response to [flu] vaccination, with digital ischemia of the hands and feet and severe fatigue." Ex. 16 at 246. Dr. Temes reported that since starting prednisone, he had experienced significant improvement in his fatigue and pain, though both persisted to a lesser degree. *Id.* He also remarked that his symptoms were exacerbated by cold exposure. *Id.* A physical

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[7] Rheumatoid factor consists of antibodies directed against antigenic determinants of immunoglobulins. *Dorland's* at 676. The presence of rheumatoid factor is associated with Type II/mixed cryoglobulinemia. J. Damoiseaux & J. Tervaert, *Diagnosis and Treatment of Cryoglobulinemia: It Takes Two to Tango*, 47 Clinical Rev. Allergy and Immunology 299, 304 (2014), filed as Ex. C (ECF No. 28-3) ("Damoiseaux").

[8] Complement levels measure the concentration of serum proteins associated with various biologic functions. *Dorland's* at 393. In cryoglobulinemia, cryoglobulins fix complement, precipitating it out of the blood serum. Tr. at 61–62.

[9] Cold agglutinins are antibodies that will agglutinate, or clump together, at lower temperatures. *Dorland's* at 38–39.

[10] Ischemia is a deficiency of blood to a part of the body, usually caused by obstruction of a blood vessel. *Dorland's* at 961.

examination showed that the discoloration of Dr. Temes's feet had completely resolved, and there was significant improvement in the appearance of his fingers. *Id.* at 250. Dr. Huber advised Dr. Temes to continue treatment with 20 mg of prednisone daily. *Id.* at 252.

At his next follow-up appointment with Dr. Huber on November 12, 2015, Dr. Temes complained of persistent pain and dry, cracked skin on his fingertips and toes, though he also noted that the appearance of ischemia had improved. Ex. 16 at 239. He also reported that his symptoms were exacerbated by the cold, and that the symptoms in his feet waxed and waned with his activity level. *Id.* Dr. Huber reviewed the laboratory test results which showed negative results for both cryofibrinogen[11] and cryoglobulin levels.[12] *Id.* at 240. Dr. Huber, however, felt that cryoglobulinemia was the proper diagnosis given Dr. Temes's clinical presentation. *Id.* at 243–44. He again advised Dr. Temes to continue 20 mg of prednisone daily, and to start taking 300 mg of Gabapentin before bed to help with his pain and fatigue. *Id.* at 244.

On November 16, 2015, Dr. Temes returned for a follow-up dermatology appointment with Dr. Callen. Ex. 2 at 9. He complained of persistent pain and a blue discoloration in his fingers and toes that had been present for approximately two weeks following receipt of the flu shot. *Id.* Though his symptoms persisted, Petitioner did report that he was experiencing improvement with prednisone. *Id.* Dr. Temes was advised to keep his feet warm and to increase his prednisone dosage from 20 mg to 40 mg a day. *Id.* Dr. Callen discussed the possibility of treating Dr. Temes with Rituxan if his condition persisted. *Id.* He also ordered additional laboratory studies. *Id.*

Dr. Huber discussed the results of those laboratory studies during a follow-up appointment with Dr. Temes on November 24, 2015. He noted that Dr. Temes's rheumatoid factor had now significantly increased, from 24 to 54. Ex. 16 at 225. During this same appointment, Dr. Temes reported improvement in his finger and toe pain, but the ischemia appeared worse following the increased prednisone dosage. *Id.* Given the lack of substantial improvement, Dr. Huber recommended Dr. Temes begin treatment with Rituxan and tapering prednisone to 30 mg a day. *Id.* at 227. Abiding by this recommendation, Dr. Temes began Rituxan treatment on December 1, 2015, but he was unable to taper his prednisone dosage without worsening pain and ischemia. *Id.* at 207.

On December 15, 2015, after two doses of Rituxan, Dr. Temes reported decreased ischemia in his fingers, though he continued to have problems with finger dexterity and required assistance with tasks such as buttoning shirts. Ex. 16 at 187. A physical examination showed considerable improvement in Dr. Temes's left foot, while his right foot continued have a dusky appearance in some of his toes. *Id.* at 190. Multiple digits on his hands also showed ischemic change and necrosis.

[11] Cryofibrinogen is a coagulation factor that precipitates in colder temperatures. *Dorland's* at 438.

[12] Through his own investigation, Dr. Temes later found that these initial laboratory findings were unreliable because the samples from which they were derived had not been properly transported to the testing facility. Tr. at 20.

Id. Given these results, Dr. Huber felt that the results of the Rituxan treatment were mixed—Dr. Temes had experienced some improvement in his left foot, but his fingers appeared to be worsening. *Id.* at 192. Dr. Huber ultimately decided that the improvement was enough to continue treatment, and on December 22, 2015, Dr. Temes received his last scheduled dose of Rituxan and his prednisone was decreased to 20 mg a day. *Id.* at 192, 161.

2016 Treatment

A few weeks later, on January 5, 2016, Dr. Temes returned to Dr. Huber for follow-up care at which time he reported improvement in his left foot and left hand, but he continued to experience necrosis in some of the fingers of his right hand as well as fairly severe pain in his right foot. Ex. 16 at 161. Dr. Temes's condition, however, showed overall improvement. *Id.* at 164. Dr. Huber therefore recommended two additional doses of Rituxan over the following two months, as well as tapering prednisone from 20 mg a day to 10 mg a day. *Id.* at 167.

During another follow-up appointment with Dr. Huber on January 19, 2016, Dr. Temes showed dramatic improvement, with nearly all of the ischemic changes having been resolved. Ex. 16 at 145. Dr. Huber reviewed the results of laboratory testing that was completed earlier that month and that showed an elevated rheumatoid factor of 24 as well as positive results for Type I cryoglobulinemia with monoclonal IgM kappa. *Id.* at 178, 183. These results effectively ruled out a differential diagnosis of Waldenström's macroglobulinemia.[13] *Id.* at 147. In light of the significant improvement, Dr. Temes was advised to continue with his Rituxan treatment, and to taper his prednisone to 5 mg daily and then, after two weeks, 5mg every other day *Id.* at 151.

On February 18, 2016, Dr. Temes received his last scheduled dose of Rituxan. Ex. 16 at 12. The next day, he returned to Dr. Ozyurekoglu for ischemia, necrosis, and ulceration in his fingers and toes. Ex. 3 at 11. Dr. Ozyurekoglu advised proper wound care and monitoring of Dr. Temes's symptoms. *Id.* at 13. One month later, on March 18, 2016, Dr. Temes returned to his primary care physician, Dr. Rogers, with weakness and sinus problems. Ex. 1 at 3. He explained that he was experiencing some pain in his hands, but that the numbness he had previously experienced had largely improved. *Id.* Following a brief examination, Dr. Rogers referred Dr. Temes to physical therapy to help alleviate the weakness caused by prolonged illness and steroid use. *Id.* at 8.

Vasculitic Symptoms and 2017 Updated Diagnosis

Over the next 15 months into the spring of 2017, Dr. Temes continued to follow up with his treating doctors. During these appointments, he reported continued improvement in his

[13] Waldenström's macroglobulinemia is a plasma cell disorder, similar to leukemia, that initiates the overproduction of macroglobulin, thereby making the blood more viscous. *Dorland's* at 1093.

symptoms, though the records indicate that he never experienced a complete remission of his symptoms. Ex. 16 at 84. Dr. Temes's overall condition, however, returned to baseline, and he was able to engage in many of the activities he had enjoyed prior to the onset of his cryoglobulinemia. *See id.* (reporting that Dr. Temes was once again able to play golf and he was doing so two to three times a week); *id.* at 89 (indicating that Dr. Temes had returned to baseline minus his continuing neuropathy). He continued to take gabapentin for his neuropathic pain, and wore sandals or loafers to alleviate any remaining discomfort. Ex. 7 at 17. During an appointment with Dr. Callen on May 3, 2016, Dr. Callen referenced a single case report of cryoglobulinemia following administration of the flu vaccine. Ex. 2 at 3. He also indicated that he was going to draft and submit a similar case report detailing Dr. Temes's clinical course. *Id.*

Petitioner's condition took a turn for the worse in 2017. In May 2017, Dr. Temes began to experience increased discomfort in his fingers and toes. Ex. 51 at 10. His pain was intermittent and induced by cold exposure, but he did not experience any ischemic changes. *Id.* He was advised to undergo further treatment with Rituxan, and he re-started treatment on May 18, 2017. *Id.* Laboratory studies conducted a few days later on May 25, 2017 showed an elevated rheumatoid factor of 36 but were negative for cryoglobulins. *Id.* at 8. Around this time, Dr. Temes also developed a rash in his feet. *Id.* at 10. A biopsy confirmed that the rash was cutaneous vasculitis, and he was instructed to taper off prednisone. *Id.* Additional laboratory testing conducted on June 26, 2017, now showed an elevated rheumatoid factor of 40 and was again positive for cryoglobulins. Ex. 51 at 8.

On June 28, 2017, Dr. Temes was evaluated at the Mayo Clinic by Dr. John Lust, M.D.[14] Ex. 19 at 14. Dr. Lust reviewed Dr. Temes's medical history as well as his more recent biopsy results, which he characterized as evidencing leukocytoclastic vasculitis.[15] *Id.* at 17. At Mayo, Dr. Temes underwent diagnostic testing including a bone marrow biopsy and CT scans.[16] *Id.* The results of the diagnostic testing confirmed a diagnosis of IgM Kapp Type II Cryoglobulinemia.[17]

[14] Though the parties appear to agree that Dr. Lust has recognized expertise in the study of cryoglobulinemia, an independent review of Dr. Lust's curriculum vitae and publications shows that he focuses much of his practice on multiple myeloma, and he is listed as a co-author on only one publication regarding cryoglobulinemia. *See generally* Mayo Clinic, *Dr. John A. Lust, M.D., Ph.D.*, https://www mayoclinic.org/biographies/lust-john-a-m-d-ph-d/bio-20053715 (last visited May 5, 2020).

[15] Leukocytoclastic vasculitis is a cutaneous vasculitis (sometimes referred to as a hypersensitivity vasculitis) attributable to dying/broken-down neutrophils that primarily affects the small vessels of the skin. It usually presents as a rash accompanied by a tingling or burning sensation. The rash may later develop lesions and/or necrosis. *Dorland's* at 2025–26.

[16] CT scans, or computed tomography, uses electronic impulses to create an image of internal structures, which is then digitally recorded. *Dorland's* at 1673.

[17] Mayo Clinic records were amended after this case was filed to reflect the subsequent diagnosis of Type II mixed cryoglobulinemia in light of the elevated rheumatoid factor levels. Ex. 49; Ex. 50.

Id.; Ex. 48 at 7. Dr. Lust recommended continuing treatment with Rituxan, and also discussed additional treatment with Cytoxan. Ex. 19 at 9. The Rituxan was discontinued on July 6, 2017, however, after Dr. Temes experienced a severe reaction during an infusion. Ex. 51 at 11; Ex. 54 at 10–11. Alternative treatment with Cytoxan was initiated on July 11, 2017, resulting in some improvement in Dr. Temes's complement levels. Ex. 51 at 1.

Dr. Temes returned to Dr. Huber for a follow-up appointment on August 3, 2017. Ex. 54 at 13. He reported that his neuropathy symptoms were stable, and that he was tolerating Cytoxan treatment well. *Id.* Dr. Huber advised Dr. Temes to continue with his prescribed treatment and follow-up care. *Id.* at 20. On September 25, 2017, laboratory testing showed a decrease in Dr. Temes's complement levels, which required an increase in his Cytoxan dosage from 100 mg to 150 mg a day. Ex. 51 at 1–2. Dr. Temes's complement levels normalized, and on November 30, 2017, a cryoglobulin screen was positive, but the confirmatory test was negative. Ex. 51 at 8.

On April 13, 2018, Dr. Temes returned to Dr. Huber for a follow-up appointment. Ex. 51 at 1. He reported that his peripheral neuropathy symptoms remained stable. *Id.* at 2. Similar to Dr. Lust's assessment, Dr. Huber noted that Dr. Temes's condition was "clinically…more consistent with a Type II cryoglobulinemia that we suspect was induced by his [flu] vaccine." *Id.* at 12. He recommended continued treatment with Cytoxan. *Id.* at 13. Dr. Temes's Cytoxan treatment was discontinued on November 5, 2019, but in February 2020, Dr. Temes's complement levels declined and Dr. Huber discussed possibly restarting Cytoxan treatment for what he suspected was another recurrence of Dr. Temes's cryoglobulinemia. Ex. 59 at 13. No further medical records were filed in this matter.

II. Witness Testimony

A. *Gerald Temes*

Dr. Temes provided testimony at the hearing consistent with the contents of his two affidavits and the filed medical record. Tr. at 4–50; Petitioner's Affidavit, filed on Feb. 2, 2017 as Ex. 15 (ECF No. 8-9); Petitioner's Supplemental Affidavit, filed on Dec. 21, 2017 as Ex. 47 (ECF No. 25-2). Dr. Temes reported that before his illness, he was active in the medical community and enjoyed participating in charity organizations, golfing, gardening, traveling, and spending time with his grandchildren prior to his October 2015 vaccinations. Tr. at 11–12. Though he admittedly had some preexisting medical conditions, Dr. Temes felt that he was overall in good health. Tr. at 14–15. Within a week of his vaccination, however, he began to develop cyanosis in his fingertips, as well as weakness, fever, muscle pain and aches. Tr. at 15.

Concerned by these symptoms, Dr. Temes sought treatment with Dr. Ozyurekoglu. Tr. at 15, 17; Ex. 3 at 1–10. Dr. Ozyurekoglu suspected Raynaud's phenomenon, but Dr. Temes sought

a second opinion from his primary care physician, Dr. Rogers. Tr. at 17–18; Ex. 1 at 16–21. Following a brief examination, Dr. Rogers concluded that Dr. Temes was experiencing coagulopathy or vasculitis, and he attributed Dr. Temes's condition to the recent flu vaccination. Tr. at 18; Ex. 1 at 20–21. He was prescribed prednisone and was referred to Dr. Huber for further assessment and treatment. Tr. at 18; Ex. 16 at 273.

During this time, Dr. Temes continued to experience pain and tingling in his legs, hands, and feet so intense that he could not sleep, and was forced to wear only light slippers or socks to limit pain to his feet. Tr. at 18, 21–22. He also noticed that his symptoms were made worse with cold exposure. *Id.* He began sleeping in a separate bedroom from his wife so that he could maintain a warmer room temperature. *Id.* at 23. He found some relief after taking these steps but continued to experience persistent symptoms of cryoglobulinemia. *Id.* The initial laboratory studies, however, were negative for cryoglobulins. *Id.* at 20. After speaking with people familiar with cryoglobulin studies, however, Dr. Temes learned that this was likely due to improper storage and transport of his blood samples. *Id.* He therefore arranged to have all further studies conducted at a local lab. *Id.*

Dr. Temes also described the Rituxan treatments that he received. Tr. at 24. After beginning treatment with Rituxan, Dr. Temes experienced some improvement in his symptoms. *Id.* at 25. But Dr. Temes suffered from discomfort that prevented him from wearing shoes (other than slippers) for another six months. *Id.* He also developed necrosis in the tips of his toes and fingers. *Id.* This symptom was unsightly and embarrassing for Dr. Temes, and he began wearing light cotton gloves and thick socks to hide the necrosis. *Id.* In addition, rather than driving to Florida as usual, Dr. Temes and his wife had to fly. *Id.* Once in Florida, however, Dr. Temes continued to heal and he noted significant improvement in his necrosis, though he continued to experience persistent pain. *Id.* at 26–27. These symptoms prevented Dr. Temes from performing many of the activities he had previously enjoyed, and he was unable to fully participate in the board positions he held within the medical community. *Id.* at 28–29. He was only able to return to playing golf once he found sandal golf shoes that left his toes exposed. *Id.* at 29.

In May 2017, Dr. Temes experienced a resurgence in his symptoms. Tr. at 29. In one particular instance, Dr. Temes was removing food from a freezer while wearing two pairs of light gloves. *Id.* at 30. Despite these precautions, Dr. Temes developed "unbearable pain" in his hands. *Id.* He returned to Dr. Huber, who concluded that Dr. Temes was experiencing a recurrence of cryoglobulinemia and recommended additional treatment with Rituxan. *Id.* This recurrence prompted Dr. Temes to seek specialized assessment and treatment from Dr. Lust at the Mayo Clinic. *Id.*

Dr. Lust's evaluation did not reveal any clear etiology for Petitioner's cryoglobulinemia. Tr. at 30–31. Dr. Lust did express his opinion, however, that the vaccines Dr. Temes received may

have played a role in the development of his condition. *Id.* at 31. Dr. Temes was advised to continue with Rituxan and to consider further treatment with Cytoxan. *Id.* But after experiencing an adverse reaction during a Rituxan infusion, Dr. Temes was advised against continuing treatment with Rituxan. *Id.* Instead, he began treatment with Cytoxan and prednisone, both of which were found to raise Dr. Temes's complement levels and reduced the severity of his symptoms. *Id.* at 31–32. He was eventually tapered off prednisone but continues to take Cytoxan every other day. *Id.* at 32. This immunosuppressive treatment prevents Dr. Temes from receiving vaccinations and makes him vulnerable to infection. *Id.* at 34.

At the time of the entitlement hearing, Dr. Temes reported that he continued to experience tingling in three fingers of his right hand, though he characterized it as "not incapacitating." Tr. at 40. He also has persistent pain in his right foot and left great toe. *Id.* at 41. He takes gabapentin for these symptoms and reports that he is doing "considerably better" and is able to perform most tasks. *Id.* at 41, 43.

B. *Petitioner's Expert – Dr. Joseph Bellanti, M.D.*

Dr. Bellanti, an immunologist, testified at hearing and filed two expert reports on behalf of Petitioner. Tr. at 51–104; Dr. Bellanti Expert Report, dated Oct. 9, 2017, filed as Ex. 20 (ECF No. 19-2) ("First Bellanti Rep."); Dr. Bellanti Supplemental Expert Report, dated May 17, 2019, filed as Ex. 52 (ECF No. 34-2) ("Second Bellanti Rep."). Dr. Bellanti opined that the flu and/or pneumococcal vaccines Petitioner received caused an inflammatory vasculitis and abnormal production of cryoglobulin—manifesting as cryoglobulinemia and, later, vasculitis. Second Bellanti Rep. at 3; Tr. at 78.

Dr. Bellanti currently serves as a professor in pediatrics and microbiology-immunology at the Georgetown University School of Medicine, as well as director of the International Center for Interdisciplinary Studies of Immunology at Georgetown University. Dr. Bellanti Curriculum Vitae, filed on Sept. 9, 2019 as Ex. 55 (ECF No. 47-2) ("Bellanti CV") at 1. He received both his bachelor's and medical degrees from the University of Buffalo before completing an internship at the Millard Fillmore Hospital in Buffalo, New York. *Id.* at 2. He then completed his residency in pediatrics at the Children's Hospital of Buffalo. *Id.* He later received specialized training in immunology at the University of Florida before serving in the United States army as a virology researcher at the Walter Reed Army Institute of Research in Washington, D.C. *Id.*; Tr. at 51–52. He is board certified in pediatrics. Bellanti CV at 3. Dr. Bellanti has also served on the editorial board of numerous journals dedicated to topics in pediatrics and immunology, and he himself has published over 300 articles on those subjects. *Id.* at 5–6, 11–65.

Dr. Bellanti began with a discussion of Dr. Temes's pre-vaccination medical history. Tr. at 55–56. None of the conditions listed in Dr. Temes's medical history, he proposed, likely

contributed to his post-vaccination condition. Tr. at 56. He then provided detailed information regarding the vaccines that Dr. Temes received on October 19, 2015. *Id.* He specifically noted that the flu vaccine administered to Dr. Temes was a "high dose" version, meaning that it contained more antigens than the average flu vaccine. *Id.* The high dose flu vaccine is meant to elicit a more robust immunologic response from elderly patients whose immune systems tend to be less responsive than those of younger patients. *Id.* at 57. Dr. Bellanti also noted that Dr. Temes received the pneumococcal vaccine at the same time the high dose flu vaccine was administered, thus further stressing Petitioner's immune response. *Id.* at 56.

Dr. Bellanti then described Dr. Temes's post-vaccination clinical course. Tr. at 57. He attributed the symptoms Dr. Temes experienced four days after vaccination—fever, aches, pain, ischemia—to an inflammatory response. *Id.* Inflammation, he explained, caused Petitioner's blood vessels to narrow and constrict, which in turn led to the ischemic changes in Dr. Temes's fingers and toes. *Id.* The fact that this vessel constriction was made worse by cold exposure is what led Dr. Bellanti to conclude that Dr. Temes suffered from cryoglobulinemia. *Id.* at 58.

Lab test results supported this conclusion, Dr. Bellanti opined, because they showed Dr. Temes had low complement levels—a result of cryoglobulin precipitate fixing complement and removing it from blood serum. Tr. at 60–62. Dr. Temes's rheumatoid factor levels were also elevated, which Dr. Bellanti cites as additional support for the diagnosis of Type II cryoglobulinemia. *Id.* at 70–71. Though Dr. Bellanti opined that Dr. Temes's cryoglobulinemia was more likely than not induced by the vaccinations he received, he acknowledged that many cases are idiopathic (and thus without a known etiology). Tr. at 86, 89. He also conceded that laboratory testing cannot distinguish between idiopathic cryoglobulinemia and cryoglobulinemia secondary to vaccine administration. *Id.* at 87–88. But even in idiopathic cases, Dr. Bellanti opined, *some* antigen-driven process is still responsible for activating the immune system and causing cryoglobulin production. Tr. at 95.

Beyond consideration of Dr. Temes's personal medical history, Dr. Bellanti's reports and testimony proposed a causation theory by which the vaccines at issue could cause cryoglobulinemia. His theory generally relied on the concept of "epigenetics," which he defined as the study of environmental influence on gene expression. Tr. at 65–66. An individual with a genetic predisposition to a particular disease, such as cryoglobulinemia, may never develop the condition unless introduced to a triggering environmental factor. *Id.* But that environmental factor may then trigger the expression or suppression of the genes responsible for the manifestation of the disease. *Id.* In Dr. Temes's case, the vaccines he received triggered the expression of certain genes responsible for the production of cryoglobulins. *Id.* at 67. Dr. Bellanti acknowledged, however, that other environmental factors, such as diet, nutrition, exposure to pollutants, and viral and bacterial infections could also provoke changes in gene expression. *Id.*

The other element of Dr. Bellanti's theory assumed that an aberrant autoimmune response could cause B cells to produce cryoglobulins essential to the development of cryoglobulinemia. Tr. at 81–82; Petitioner's Post-Hearing Brief, filed Nov. 21, 2019 (ECF No. 54) at 5. To support this aspect of his opinion, Dr. Bellanti cited to a study from the 1960s that observed the effects of hyperimmunizing rabbits with a pneumococcal vaccine. E. Catsoulis et al., *Cryoglobulinemia in Rabbits Hyperimmunized with a Polyvalent Pneumococcal Vaccine*, 9 Immunology 327, 327–331 (1965), filed on Oct. 16, 2017 as Ex. 22 (ECF No. 19-4) ("Catsoulis"). Catsoulis found that administering the pneumococcal vaccine to rabbits every three days induced cryoglobulinemia within three to four months. *Id.* at 327. Importantly, the cryoglobulins that were produced were found to agglutinate (or cluster)[18] pneumococci—the bacteria against which the rabbits had been immunized. *Id.* This fact, according to Dr. Bellanti, established that the cryoglobulins possessed an antibody-like capacity that could then become harmful as they became overexpressed in the blood. First Bellanti Rep. at 3. When the animal subjects were no longer vaccinated, they recovered within five weeks. Catsoulis at 327, 330. Re-initiation of the vaccine, by contrast, resulted in a recurrence of cryoglobulinemia—peaking within three to five weeks of re-exposure to the pneumococcal vaccine. *Id.* Catsoulis thus concluded that intense immunization could stimulate the production of cryoglobulins. *Id.*

Here, there is no similar evidence that Dr. Temes underwent repeated vaccination comparable to the tested animals in Catsoulis—and thus there is a question as to how cryoglobulinemia akin to what Petitioner experienced could become chronic. Dr. Bellanti therefore invoked other potential autoimmune mechanisms, including molecular mimicry and bystander activation, to explain how cryoglobulinemia could persist. Tr. at 101. Dr. Bellanti did not provide robust discussion for either of these theories, but he did (though perhaps inadvertently) offer two different explanations regarding bystander activation. First, Dr. Bellanti indicated that following the initial activation of the immune system, nearby immune cells not initially participating in that response can be activated and contribute to ongoing inflammation, thereby causing it to continue. Tr. at 101. He later proposed an alternative theory of bystander activation, in which damaged cells resulting from cryoglobulinemia and leukocytoclastic vasculitis act *themselves* as antigens that independently but directly cause an autoimmune response, sufficient to promote chronicity of the underlying condition. Tr. at 103.

Despite the above, Dr. Bellanti's opinion largely relied on a series of case reports identifying instances of vasculitis, cold contact urticaria, and cryoglobulinemia following vaccination—though his discussion of each report was brief. Tr. at 74–78. The first of these reports described four cases of leukocytoclastic vasculitis following receipt of the flu vaccine. S. Tavadia et al., *Leukocytoclastic Vasculitis and Influenza Vaccination*, 28 Clinical and Experimental Dermatology 154, 154–56 (2003), filed Apr. 7, 2020 as Ex. 23 (ECF No. 57-1) ("Tavadia"). Of

[18] *Dorland's* at 38–39.

the four case reports discussed in Tavadia, Dr. Bellanti focused his testimony on one in which a seventy-one-year-old woman developed leukocytoclastic vasculitis following receipt of the flu vaccine two weeks later. *Id.* at 154. This case was of particular interest to Dr. Bellanti because it appeared to involve the first flu vaccine the woman had received (meaning her response could not have constituted a rechallenge event)—though the case report itself does not confirm that the woman had not previously received a flu shot. Tr. at 75; Tavadia at 154. Overall, Dr. Bellanti characterizes the case reports discussed in Tavadia as "very similar to what Dr. Temes experienced." Tr. at 75.

Dr. Bellanti next discussed a single case report in which the authors described a patient who experienced onset of cutaneous vasculitis and exacerbation of preexisting rheumatoid arthritis two weeks after receiving the flu vaccine. P. Iyngkaran et al., *Rheumatoid Vasculitis Following Influenza Vaccination*, 42 Rheumatology 907, 907–909 (2003), filed on Apr. 7, 2020 as Ex. 24 (ECF No. 57-2) ("Iyngkaran"). While the temporal relationship between the vaccination and onset of the patient's vasculitis suggested a possible cause-and-effect relationship, Iyngkaran was unable to identify a specific mechanism capable of supporting such a conclusion. Iyngkaran at 909.

Dr. Bellanti then pivoted to four case reports documenting the development of cold contact urticaria[19] following vaccination. N. Raison-Peyron et al., *Cold Contact Urticaria Following Vaccination: Four Cases*, 96 Acta Dermato-Venereologica 852, 852–53 (2016), filed on Oct. 16, 2017 as Ex. 25 (ECF No. 19-7) ("Raison-Peyron"). Only one of the cases documented in Raison-Peyron involved a vaccine that Dr. Temes received, however (pneumococcal), and that case involved a two-year old whose urticaria began seven days after receipt of it plus several other vaccines. *Id.* at 852. At hearing, however, Dr. Bellanti primarily focused on the case report documenting the development of cold contact urticaria in a thirty-seven-year-old woman three weeks after receiving the Pandemrix vaccine (a vaccine that never has been administered in the U.S.)[20] against the 2009 H1N1 influenza strain. Raison-Peyron at 853.

Another reason to give limited weight to such case reports, as Dr. Bellanti admitted, is the fact that cold contact urticaria and cryoglobulinemia are distinguishable. Tr. at 77. Indeed, the laboratory findings discussed in Raison-Peyron did not reveal any abnormalities, whereas mixed/Type II cryoglobulinemia is characterized by low complement levels, elevated rheumatoid factor, and elevated cryoglobulin levels. Raison-Peyron at 852–83; *see also* A. Lohse et al., *Vascular Purpura and Cryoglobulinemia After Influenza Vaccination*, 66 Rev. Rheumatology 359, 359–62 (1999), filed on Oct. 16, 2017 as Ex. 26 (ECF No. 19-8) ("Lohse"). Thus, although Raison-

[19] Cold contact urticaria causes an individual to develop hives when their skin is exposed to cool temperatures. *Dorland's* at 2012; Raison-Peyron at 852.

[20] S*ee generally*, *D'Toile v. Sec'y of Health & Human Servs.*, No. 15-085V, 2016 WL 7664475 (Fed. Cl. Spec. Mstr. Nov. 28, 2016) (discussing the use of Pandemrix in Europe), *mot. for review den'd*, 132 Fed. Cl. 421 (2017)), *aff'd,* 726 F. App'x 809 (Fed. Cir. 2018).

Peyron's authors expressed concerns regarding the possibility of a causal relationship between vaccination and cold contact urticaria, they were unable to identify a specific causal mechanism, noting that "the mechanisms and signals for cold-dependent mass cell activation have not been identified." Raison-Peyron at 853.

Lastly, Dr. Bellanti mentioned a single case report of a sixty-eight-year-old man who developed Type II mixed cryoglobulinemia two weeks after receiving the flu vaccine. Tr. at 77–78; Lohse at 359. But like the other case reports referenced by Dr. Bellanti, this case report mostly relied on a temporal association between vaccination and disease manifestation, ultimately concluding that "[t]he mechanism of vasculitis induced by [flu] vaccination remains incompletely understood….[t]hus in none of the reported cases was proof of a causal link with the [flu] vaccine obtained." Lohse at 359.

C. *Respondent's Expert – Dr. Harry Schroeder, Jr., M.D., PhD*

Dr. Schroeder testified at hearing and provided two expert reports on behalf of Respondent. Tr. at 105–68; Dr. Schroeder Expert Report, dated Mar. 30, 2018, filed as Ex. A (ECF No. 28-1) ("First Schroeder Rep."); Dr. Schroeder Supplemental Expert Report, dated July 11, 2018, filed as Ex. G (ECF No. 37-1) ("Second Schroeder Rep."). He opined that Dr. Temes's cryoglobulinemia was most likely unrelated to the vaccines he received. Tr. at 110–11.

Dr. Schroeder is board certified in both internal medicine and genetics. Dr. Schroeder Curriculum Vitae, filed on Apr. 6, 2018, as Ex. B (ECF No. 28-2) ("Schroeder CV") at 4. He received his bachelor's degree from Texas A&M University, before receiving both his medical degree and PhD from Baylor College of Medicine. *Id.* at 1. Dr. Schroeder then completed his internship and residency at the University of Kentucky Medical Center. *Id.* at 2. Since 2008, he has taught as a professor of medicine, microbiology, and genetics at the University of Alabama where he also serves as the director of the immunology program. Tr. at 105. Dr. Schroeder's clinical practice as an immunologist began in 1991. Tr. at 107. He sees patients with a wide range of immunological disorders, including autoimmune, hypersensitivity, and immunodeficiency disorders. First Schroeder Rep. at 1. The majority of Dr. Schroeder's time is spent conducting research in immunology and the role of genetics in immunological disorders and treatments. Schroeder CV at 8–23. He has also published numerous articles on these subjects. *Id.* at 24–33. However, though much of Dr. Schroeder's career has focused on immunology, he is not board certified in the subject, and he does not have expertise or specialized training related to cryoglobulinemia. Tr. at 109, 132–33.

At hearing, Dr. Schroeder began by contesting Petitioner's success in establishing how the relevant vaccines might cause cryoglobulinemia. He specifically criticized Dr. Bellanti's theory regarding epigenetics to explain how vaccination might interact with some unknown or undefined

predisposition, evaluating it in light of what is known about the condition. Tr. at 113–16. Cryoglobulinemia, Dr. Schroeder observed, in its Type I form is associated with abnormal B cells produced as a result of persistent malignant conditions, like multiple myeloma and Waldenström's macroglobulinemia. Tr. at 115. Although Dr. Schroeder did not disagree that Petitioner had properly been diagnosed with Type II, or "mixed" cryoglobulinemia (which features the additional element of elevated rheumatoid factor lab findings), the underlying product of altered B cells would still be featured. *Id.* at 114–16. In either case, Dr. Bellanti's epigenetics theory relied on the conclusion that B cell alteration can also be caused by environmental triggers such as vaccination. Tr. at 64–67. But Dr. Schroeder noted an absence of reliable scientific evidence to suggest that the flu virus or vaccination can directly result in B cell mutations. *Id*. at 116.

In so maintaining, Dr. Schroeder rejected the probative value of the limited literature offered by Petitioner. Lohse, for example, expressly avoided concluding that vaccine causality was established by its findings from the case studies it considered. Tr. at 126 (citing Lohse at 359 (finding that a relationship between vaccination and cryoglobulinemia could not be confirmed)). Catsoulis was similarly unpersuasive in Dr. Schroeder's estimation. *Id.* at 111–13. The hyperimmunization achieved in Catsoulis could not be induced by the administration of a single high dose flu vaccine like that received by Dr. Temes. *Id.* at 111. Therefore, the effects of hyperimmunization observed in Catsoulis—the production of cryoglobulins—could not have resulted from Dr. Temes's vaccination. *Id.*

Dr. Schroeder also discussed whether Dr. Temes's leukocytoclastic vasculitis diagnosed in 2017 could be vaccine-attributed, as a secondary result of cryoglobulinemia first observed fifteen months earlier. Tr. at 125–29, 146–53, 155, 160–65. He emphasized that the literature offered by Petitioner to support the proposition that vaccines can cause vasculitis did not involve patients *first* suffering from cryoglobulinemia. Tr. at 163–65 (citing S. Monjazeb et al., *A Case of Leukocytoclastic Vasculitis Following Influenza Vaccination*, 2 JAAD Case Reports 340, 340–42 (2016), filed Sept. 16, 2019 as Ex. 56 (ECF No. 48-2) ("Monjazeb"); B. Fox & A. Peterson, *Leukocytoclastic Vasculitis After Pneumococcal Vaccination*, 26 AJIC 365, 365–66 (1998), filed Sept. 16, 2019 as Ex. 57 (ECF No. 58-3) ("Fox")).

Dr. Temes's vasculitis, by contrast, was *secondary* to the cryoglobulins precipitating in his blood, and thus did not itself reflect a direct vaccine injury as discussed in such articles. Tr. at 125. Dr. Schroeder also observed that the supposed connection between vaccination and vasculitis as a general matter was itself not reliably supported, citing a comprehensive literature review analyzing seventy-five studies that concluded that no causal relationship could be confirmed with existing data. C. Bonetto et al., *Vasculitis as an Adverse Event Following Immunization – Systemic Literature Review*, Vaccine 1, 8 (2015), filed as Ex. E (ECF No. 28-5) ("Bonetto"). Additionally, proposed diagnostic criteria for "cryoglobulinemia vasculitis" includes the presence of leukocytoclastic vasculitis, further suggesting that clinical manifestations of vasculitis under such

circumstances were dependent on the pre-existence of cryoglobulinemia. Damoiseaux at 305.

Regarding the onset of Petitioner's condition, Dr. Schroeder opined that clinical evidence appearing within a week of vaccination, as here, was too quick to establish a causal relationship between the two. Tr. at 122–23, 158. Rather, it would take approximately two to three weeks for an adequate concentration of immunoglobulins to build up in the body before symptoms of cryoglobulinemia would manifest. *Id.* Instead, he proposed the possibility that Dr. Temes's initial onset was the result of October's cooler temperatures in Kentucky where Dr. Temes resides—though Dr. Schroeder was unable to confirm that Dr. Temes's cryoglobulinemia likely pre-dated his vaccination. *Id.* at 123, 157. Dr. Schroeder also admitted that his views on timing had not been set out in his original reports. *Id.* at 139–44.

While Dr. Schroeder largely opposed the opinions of Dr. Bellanti, there were several points on which both experts agreed. First, Dr. Schroeder agreed that Petitioner's condition was properly diagnosed as Type II mixed cryoglobulinemia, despite initial reports and medical records documenting a diagnosis of Type I cryoglobulinemia. Tr. at 125, 142, 166. He also acknowledged that several of Dr. Temes's treating physicians expressed the opinion that his condition was related to the vaccinations that he received in October 2015. Tr. at 128, 158–59. He did not, however, find this treater support persuasive due to the lack of confirmatory studies. *Id.* Lastly, after expressing some skepticism (Tr. at 125, 146), Dr. Schroeder ultimately agreed that Petitioner later experienced leukocytoclastic vasculitis secondary to his cryoglobulinemia. Tr. at 152, 165.

III. Procedural History

As previously noted, this matter commenced with the filing of the Petition on November 7, 2016. Over the following months, Petitioner filed medical records in support of his claim. Respondent thereafter filed a Rule 4(c) Report on May 25, 2017, asserting that compensation is not appropriate in this case. Respondent's Report, filed May 25, 2017 (ECF No. 15). Petitioner subsequently filed a report from Dr. Bellanti and supporting literature on October 16, 2017. Respondent filed a responsive report by Dr. Schroeder on April 6, 2018, along with literature in opposition to Petitioner's position. Both Petitioner and Respondent then filed supplemental expert reports on May 25, 2018 and July 13, 2018 respectively. The parties filed their respective pre-hearing briefs over the summer of 2019, and a one-day entitlement hearing took place on September 10, 2019. The parties elected to file post-hearing briefs, which they did on November 21, 2019, and the matter is fully ripe for resolution.

IV. Applicable Law

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[21] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] 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.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

[21] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

Each of the *Althen* prongs requires a different kind of evidentiary showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355–56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury.

In discussing the evidentiary standard applicable to the first *Althen* prong, the Federal Circuit has consistently rejected the contention that it can be satisfied merely by establishing the proposed causal theory's scientific or medical plausibility. *See Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019); *see also LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[h]owever, in the past we have made clear that simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." (citing *Moberly*, 592 F.3d at 1322)). Petitioners otherwise always have the ultimate burden of establishing their *overall* Vaccine Act claim with preponderant evidence, regardless of what evidentiary level of evidence on the "can cause" prong is required. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell*, 133 Fed. Cl. at 793 (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance standard).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly

trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

Medical records and statements of a treating physician, however, do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. Appx. 765 (Fed. Cir. 2012).

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

B. *Legal Standards Governing Factual Determinations*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained

in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd sub nom. Rickett v. Sec'y of Health & Human Servs*., 468 F. Appx. 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs.*, No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony—especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Dep't of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

There are, however, situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("'[w]ritten records which are, themselves, inconsistent, should be accorded less deference than

those which are internally consistent'") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *Lalonde v. Sec'y of Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health*

& Human Servs., 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Expert opinions based on unsupported facts may be given relatively little weight. *See Dobrydnev v. Sec'y of Health & Human Servs.*, 556 F. Appx. 976, 992–93 (Fed. Cir. 2014) ("[a] doctor's conclusion is only as good as the facts upon which it is based") (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993) ("[w]hen an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion")). Expert opinions that fail to address or are at odds with contemporaneous medical records may therefore be less persuasive than those which correspond to such records. *See Gerami v. Sec'y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013), *aff'd*, 127 Fed. Cl. 299 (2014).

D. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all the medical literature submitted

in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. Appx. 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

E. *Consideration of Comparable Special Master Decisions*

In reaching a decision in this case, I have considered other decisions issued by special masters (including my own) involving similar injuries, vaccines, or circumstances. I also reference some of those cases in this Decision, in an effort to establish common themes, as well as demonstrate how prior determinations impact my thinking on the present case.

There is no error in doing so. It is certainly correct that prior decision in different cases do not *control* the outcome herein.[22] *Boatmon v. Sec'y of Health & Human Servs.,* 941 F.3d 1351, 1358–59 (Fed. Cir. 2019); *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). Thus, the fact that another special master reasonably determined elsewhere, on the basis of facts not in evidence in this case, that preponderant evidence supported the conclusion that vaccine X caused petitioner's injury Y does not compel me to reach the same conclusion in *this* case. Different actions present different background medical histories, different experts, and different items of medical literature, and therefore can reasonably result in contrary determinations.

However, it is *equally* the case that special masters reasonably draw upon their experience in resolving Vaccine Act claims. *Doe v. Sec'y of Health & Human Servs.,* 76 Fed. Cl. 328, 338–39 (2007) ("[o]ne reason that proceedings are more expeditious in the hands of special masters is that the special masters have the *expertise and experience to know the type of information that is most probative of a claim*") (emphasis added). They would therefore be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions. This is especially so given that special masters not only routinely hear from the same experts in comparable cases but are also repeatedly offered the *same* items of medical literature regarding certain common causation theories. It defies reason and logic to obligate special masters to "reinvent the wheel", so to speak, in each new case before them, paying

[22] By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014). Special masters are also bound within a specific case by determinations made by judges of the Court of Federal Claims after a motion for review is resolved.

no heed at all to how their colleagues past and present have addressed similar causation theories or fact patterns. It is for this reason that prior decisions can have high persuasive value—and why special masters often explain how a new determination relates to such past decisions.[23] Even if the Federal Circuit does not *require* special masters to distinguish other relevant cases (*Boatmon,* 941 F.3d at 1358), it is still *wise* to do so.

ANALYSIS

I. Overview of Cryoglobulinemia

The experts largely agreed on the characteristics of cryoglobulinemia, but a few additional points are in order. Cryoglobulinemia is a condition in which particular serum antibodies called "cryoglobulins" reversibly precipitate in the blood when cooled below 37 degrees Celsius (98.8 degrees Fahrenheit). Damoiseaux at 299. As a result, complex deposits form in the blood vessels, causing the blood to become more viscous. *Id.* at 299, 302. These deposits and the increased blood viscosity may result in vascular occlusion and other vasculitic harm. *Id.*

Because there are three subtypes of cryoglobulinemia, careful differentiation can provide useful information regarding potential etiologies and treatment options. Type I is typically associated with lymphoproliferative diseases and monoclonal IgM.[24] Damoiseaux at 299–300. Type II, or "mixed" cryoglobulenimia is thought to be caused by systemic autoimmune or infectious disease, and features monoclonal IgM, polyclonal IgG, and rheumatoid factor activity. *Id.* Type II is particularly associated with a hepatitis C infection. Damoiseaux at 303. Type III, which is also associated with autoimmune and infectious processes, may consist of monoclonal IgM, polyclonal IgG, and/or polyclonal IgA in any combination and may also feature rheumatoid factor activity. *Id.* Types II and III are characterized by the formation of immune complexes and are therefore called mixed cryoglobulins. *Id.* at 300. In this case, there is no dispute that Dr. Temes most likely had Type II cryoglobulinemia, given his rheumatoid factor findings, although the record does not suggest he was ever found to possess an intercurrent hepatitis C infection. Tr. at 70–71, 98. 142, 144–45.[25]

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[23] Consideration of prior determinations is a two-way street that does not only inure to the benefit of one party. Thus, I would likely take into account the numerous decisions finding no association between vaccination and autism when confronted with a new claim asserting autism as an injury and have informed such claimants early in the life of their case that the claim was not viable for just that reason. But I would *also* deem a non-Table claim asserting GBS after receipt of the flu vaccine as not requiring extensive proof on *Althen* prong one "can cause" matters, for the simple reason that the Program has repeatedly litigated the issue in favor of petitioners.

[24] IgM is a specific class of immunoglobulins and is involved in the activation of complement pathways as well as the initiation of phagocytosis of bound antigens. *Dorland's* at 913, 919.

[25] This agreement was reached only after Dr. Temes's treating physician, Dr. Lust, was asked to reevaluate Dr. Temes's diagnosis in light of Dr. Schroeder's initial expert report, which noted that Dr. Lust had diagnosed Dr. Temes

While the serological differences between the subtypes is helpful in distinguishing between them, their clinical manifestations will also differ and can provide further diagnostic clarity. Symptoms of Type I cryoglobulinemia include Raynaud's phenomenon, peripheral necrosis, increased blood viscosity, and vascular occlusion—though in some cases vasculitis may also occur. Damoiseaux at 302. It is commonly comorbid with Waldenström's macroglobulinemia, monoclonal gammopathy of unknown significance, or some other lymphoproliferative disease. *Id.* Type II cryoglobulinemia, by contrast, often manifests as cutaneous vasculitis and peripheral neuropathy. *Id.* In mixed cryoglobulinemia (Type II or III) the immune complexes that form will interact with complement, thereby interfering with the biological pathways controlled by complement proteins. *Id.* at 304. Therefore, measuring complement levels—especially that of C4—is particularly helpful in the diagnosis and management of mixed cryoglobulinemia. *Id.* The presence of rheumatoid factor also distinguishes mixed cryoglobulinemias from Type I. *Id.*

Treatment of cryoglobulinemia is ill-defined. Where an underlying disease process results in cryoglobulinemia, such as with lymphoproliferative diseases, treatment of the underlying disease is the first treatment option employed. Damoiseaux at 306. In mixed cryoglobulinemias with unknown etiology, by contrast, treatment may be more varied, and may include nonsteroidal anti-inflammatory drugs or short-term corticosteroids. *Id.* Avoidance of cold temperatures is also recommended. *Id.* For patients who experience relapses in their symptoms, Rituximab (Rituxan) appears to be an effective treatment. *Id.*

While cryoglobulinemia has not been alleged as a vaccine injury in prior Program cases, vasculitic injuries are commonly alleged and have been litigated with varying degrees of success. *See, e.g.*, *Bourche v. Sec'y of Health & Human Servs.*, No. 15-232V, 2020 WL 571061 (Fed. Cl. Spec. Mstr. Jan. 7, 2020) (denying entitlement where the alleged injuries included leukocytoclastic vasculitis after receiving the hepatitis B vaccine); *Guzman v. Sec'y of Health & Human Servs.*, No. 15-736V, 2019 WL 2723392 (Fed. Cl. Spec. Mstr. May 14, 2019) (denying entitlement where petitioner alleged cutaneous vasculitis following receipt of the flu vaccine); *but see McElroy v. Sec'y of Health & Human Servs.*, No. 11-679V, 2012 WL 1739873 (Fed. Cl. Spec. Mstr. Apr. 13, 2012) (finding that petitioner was entitled to compensation after providing preponderant evidence that the flu vaccine caused her to develop urticaria vasculitis within a few days to a week after).

with Type I cryoglobulinemia—the subtype *least* likely to be associated with an autoimmune or infectious disease process (and therefore far less likely to be vaccine-caused). See Ex. 50; First Schroeder Rep. at 7. Dr. Lust subsequently revised his diagnosis and explained that due to the presence of rheumatoid factor, Dr. Temes's condition was best classified as Type II mixed cryoglobulinemia. Ex. 50. Thus, although it could be inferred that some of the impetus to modify Petitioner's original diagnosis was to support the present claim, the fact that both experts have accepted it, and that it has evidentiary support, means that the new diagnosis has been preponderantly established.

II. Petitioner has Not Preponderantly Supported His Burden in Proving Causation

A. *Petitioner Has Not Offered a Scientifically-Reliable Causation Theory* (*Althen Prong One)*

As a threshold matter, I note that Petitioner erroneously argues for an evidentiary standard of mere plausibility in evaluating his success in establishing the "can cause" prong of the *Althen* test. Pet. Post-Hearing Brief at 5 ("Petitioner's *plausible* theory of causation presented is that, the vaccination alone, or in combination with a compromised immune system triggered an abnormal response in Dr. Temes, which caused him to develop Type II Cryoglobulinemia within a medically acceptable time frame." (emphasis added)). Such a standard has consistently been rejected by the Federal Circuit. *Boatmon*, 941 F.3d at 1359 (rejecting the "plausibility" standard). Rather, special masters are tasked with determining whether the proffered theory is "reputable," or "sound and reliable." *Id.* While the preponderant standard set by the Vaccine Act does not mandate medical certainty, it also does not permit recovery simply based on the reasonable-sounding nature of a particular theory. Applying the correct standard, I find that Petitioner has failed to proffer a medically or scientifically *reliable* theory of causation as is required under the first *Althen* prong.

First, Petitioner over-relies on assumptions about the interplay of vaccination with genetic susceptibility to cryoglobulinemia that the evidence does not support. Dr. Bellanti proposed that vaccines could trigger malfunction in the expression of genes responsible for cryoglobulin production. Tr. at 67. He did not, however, identify the genes responsible for cryoglobulin production, discuss which vaccine components could trigger or silence gene expression, and did not offer persuasive evidence showing that any vaccines, the specific ones at issue, or even the wild virus or bacterial antigens underlying those vaccines have this capacity. *Id.* at 64 ("[T]he vaccine that caused this abnormal reduction of this gammaglobulin called cryoglobulin. Why that occurs, we don't have all the answers"). Indeed, Dr. Bellanti allowed that *other* environmental factors (e.g., exposure to pollutants) could also cause alterations in gene expression (thus complicating the assertion that vaccines would more likely explain this event), and that because gene expression will change throughout a person's lifetime, it was conceivable that such changes predated a given vaccination event. None of the literature offered in this case otherwise acknowledged epigenetics as a potential mechanism through which an individual may develop cryoglobulinemia, regardless of trigger.

The second step of Petitioner's proffered theory proposed that an immunocompromised state (resulting from the above referenced epigenetic changes) allowed vaccination to initiate the abnormal production of cryoglobulins. Tr. at 73–74; Petitioner's Post-Hearing Brief, filed Nov. 21, 2019 (ECF No. 54) ("Pet. Post-Hearing Brief") at 5. Relying particularly on Catsoulis, Petitioner argues that pneumococcal vaccines can invoke cryoglobulin production. Pet. Post-Hearing Brief at 5; Catsoulis at 327. However, Catsoulis's probative value is limited. Not only was

its study conducted over fifty years ago (and thus its findings lack recent corroboration or follow-up), but Catsoulis found that cryoglobulin production was induced in animal subjects *only after* hyperimmunization over the course of months. Catsoulis at 327 (explaining that the rabbits were immunized every three days, and usually thereafter developed cryoglobulins within three to four months). It also noted that the particular cryoglobulins were specific to the antigen causing the agglutination (pneumococci), and yet this has not been demonstrated to have occurred in Dr. Temes's case. *Id.* Accordingly, although Catsoulis does suggest that the pneumococcal vaccine could cause cryoglobulin formation, it does so under circumstances that are not comparable to a single-instance receipt of the vaccine.

The evidence that the flu vaccine could similarly induce cryoglobulin production, by contrast, lacked any similar evidentiary support, and was only vaguely supported in Petitioner's case. Pet. Post-Hearing Brief at 7; Tr. at 56–57, 64, 73–74. At best, Dr. Bellanti appears to have assumed that the same hyperimmunization effect was possible when dealing with a high-dose version of the vaccine comparable to what was administered in this case. Pet. Post-Hearing Brief at 7; Tr. at 56, 64. This contention was not supported with more than conclusory statements (again rooted in a conception of plausibility as sufficient to meet the Program's evidentiary standards), and a single high dose flu vaccine is unlikely to produce results similar to those seen in Catsoulis, which required roughly *thirty to forty* immunizations to induce cryoglobulinemia. Catsoulis at 327; Tr. at 111.

Petitioner also sought to establish a causal relationship between the flu vaccine and cryoglobulinemia by invoking case reports of post-vaccination vasculitis (and in particular leukocytoclastic vasculitis). *See generally* Pet. Post-Hearing Brief at 8. In so doing, Petitioner reasoned that because cryoglobulinemia can result in the subsequent development of leukocytoclastic vasculitis, then a causal relationship likely also exists between vaccines and cryoglobulinemia. Tr. at 146–53, 160–62, 165; *see generally* Tavadia; Monjazeb; Fox.

There are, however, several flaws with this argument. First, none of the referenced case reports confirmed a causal relationship between vaccination and the subsequent development of leukocytoclastic vasculitis in the first place. *See, e.g.*, Monjazeb at 341 ("[t]he temporal nature of these cases of vasculitis following vaccination suggest an immunopathogenic link that has yet to be explained."). Second, the primary "injury" in this case is Type II cryoglobulinemia—not leukocytoclastic vasculitis, which can occur independently—and it is well understood in the Program that establishing that a vaccine can cause a comparable injury is not especially strong support for the contention that it caused the injury *at issue*. *See, e.g.*, *Hunt v. Sec'y of Health & Human Servs.*, No. 12-232V, 2015 WL 1263356, at *15 (Fed. Cl. Spec. Mstr. Feb. 23, 2015) (denying entitlement where MS was the alleged injury, but the literature offered discussed causal relationship between vaccines and acute disseminated encephalomyelitis). With the exception of Lohse, none of the cited case reports observing temporal association between leukocytoclastic

vasculitis and vaccination mentioned cryoglobulinemia as occurring first. While Lohse suggests that cryoglobulinemia and hypersensitivity vasculitides such as leukocytoclastic vasculitis may develop simultaneously, it does not describe how an initial onset of cryoglobulinemia can produce leukocytoclastic vasculitis years later, as in Dr. Temes's case. *See* Lohse at 359.

Third, the general fact that some probative evidence exists for the proposition that a vaccine can cause a secondary condition does not inexorably lead to the conclusion that it can also be causal of the preceding injury or illness. To give but one possible example, paraneoplastic syndrome can occur as the consequence of a cancerous tumor in the body, stimulating aberrant immune responses that can result in disease processes, such as Guillain-Barré syndrome ("GBS"). GBS is itself understood to be vaccine-caused in some rare instances—but this does not mean that vaccines can *also* cause the tumor giving rise to the syndrome. *See, e.g.*, *Sweeney v. Sec'y of Health & Human Servs.*, No. 13-392V, 2020 WL 1844672, at *20–23 (Fed. Cl. Spec. Mstr. Feb. 28, 2020) (providing extensive discussion regarding the relationship between paraneoplastic syndrome and GBS).

Finally, Petitioner's explanation for how a one-time vaccination event could result in a chronic condition was also scientifically unreliable. To substantiate this aspect of his causation theory, his expert Dr. Bellanti relied on two biologic mechanisms—molecular mimicry and bystander activation. Tr. at 101. But neither were persuasively shown to have more than theoretical applicability in this case.

Molecular mimicry is a mechanistic explanation for an autoimmune process, wherein the immune system of an individual reacts to self-structures as well as a foreign antigen because the self-structures are sufficiently similar in molecular composition to the foreign antigen that the immune system is unable to distinguish between the two. *See, e.g.*, *Stewart v. Sec'y of Health & Human Servs.*, No. 06-777V, 2011 WL 3241585, at *16 (Fed. Cl. Spec. Mstr. July 8, 2011) (concluding that molecular mimicry was a reliable scientific theory explaining how the flu vaccine could cause GBS, based on submitted literature and expert testimony identifying specific homology between the myelin sheath and components of the flu vaccine). But beyond conclusory statements by Dr. Bellanti, no reliable literature was offered to suggest that the relevant vaccines can trigger such a process in causing persistent cryoglobulinemia.[26]

Dr. Bellanti's characterizations of bystander activation as possibly explaining the persistence of a vaccine-caused cryoglobulinemia were no better supported, and in fact were inconsistent. When he first described bystander activation, Dr. Bellanti indicated that following the initial activation of the immune system, nearby cells not directly implicated in the initial

[26] There is some evidence that chronic hepatitis C infections may cause cryoglobulinemia through the mechanistic process of molecular mimicry. Damoiseaux at 303. This is because monoclonal IgM rheumatoid factor in mixed cryoglobulinemias share substantial homology with outer layer of the hepatitis C virus. *Id.* Evidence of similar homologies in either the flu virus or *Streptococcus pneumoniae* bacterium was not offered in this case.

response are activated and can thereby perpetuate the inflammatory response. Tr. at 101. But he went on to maintain that bystander activation occurs when antigens destroy cellular structures, causing the destroyed cells to *themselves* become antigenic. *Id.* at 103. Although the former version has been deemed scientifically reliable (*see, e.g.*, *Bender v. Sec'y of Health & Human Servs.*, No. 11-693V, 2018 WL 3679637, at *7–8, *28 (Fed. Cl. Spec. Mstr. July 2, 2018) (discussing the theory of bystander activation at length but ultimately rejecting it as a reliable theory of causation)), Dr. Bellanti did not substantiate his contention with either independent literature or his own personal experience and research to show that cryoglobulinemia is known to become chronic in this manner.

The more fundamental deficiency with Petitioner's arguments about how his disease process became chronic is based in what *is* known about cryoglobulinemia. As Dr. Schroeder explained, IgM antibody production increases three to four weeks post-vaccination, but then declines as B cells responsible for the production of these antibodies expire. Tr. at 114. Only ongoing exposure to an antagonizing antigen will perpetuate IgM production (and this usually occurs in cases of Type II/mixed cryoglobulinemia as a result of a persistent hepatitis C infection). *See* Tr. at 114, 121; Damoiseaux at 303. But Petitioner did not offer any evidence to suggest that the antigenic components of the flu and/or pneumococcal vaccines remained present and active in the body for a sufficiently prolonged period to produce the same chronic effects. *Id.* at 122.[27]

With the relatively sparse evidentiary support for Petitioner's arguments relating to epigenetics, hyperimmunization, molecular mimicry, and bystander activation, Petitioner's theories were ultimately too conclusory and incomplete to be deemed preponderantly reliable. The lack of credible and persuasive evidence on the issue of causation leads me to conclude that Petitioner has not satisfied the first *Althen* prong. Though I found Dr. Bellanti was more qualified to opine on the presented topics overall, his theories were too thin and relied too heavily upon case reports to successfully carry Petitioner's burden. Although Respondent may not have persuasively rebutted Petitioner's assertions as a whole, Petitioner nevertheless failed at the outset to provide preponderant evidence in support of his proposed theories regarding causation.

B. *Treater Conclusions About Vaccine Causation Alone Were Not Enough By Themselves to Satisfy the Second Althen Prong*

The second *Althen* prong requires petitioners to preponderantly establish that the vaccine in question *did cause* the alleged injury. *Althen*, 418 F.3d at 1278. The medical record in this case does contain some favorable evidence on this point, mainly in the form of statements made by several of Dr. Temes's treating physicians in which they expressed the opinion that his

[27] I also take note of the relevance of rheumatoid factor in Type II cryoglobulinemia. The record indicates that Petitioner was found early on to possess this biomarker. *See, e.g.*, Ex. 16 at 178, 273. Petitioner did not propose, however, that the vaccines he received caused this to occur.

cryoglobulinemia was the result of the vaccinations he received. Ex. 2 at 12; Ex. 16 at 277. Indeed, Dr. Callen, Dr. Temes's treating dermatologist, recently co-authored a case report describing Dr. Temes's clinical course and observing the (at least temporal) association between the vaccines and Petitioner's onset. S. Eid & J. Callen, *Type II Mixed Cryoglobulinemia Following Influenza and Pneumococcal Vaccine Administration*, 5 JAAD Case Reports 960, 962 (2019), filed as Ex. 58 (ECF No. 52-2) ("Callen Case Report"). Such evidence is worthy of *some* weight.

It is, however, well understood in the Program that I am not bound by treater opinions, especially when other evidence rebuts or contradicts the grounds for such views. *Snyder*, 88 Fed. Cl. at 746 n.67 ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Here, and as previously discussed, none of the literature filed in this matter supported a causal relationship between vaccination and the subsequent development of cryoglobulinemia. Nor did Dr. Bellanti substantiate his opinions with reference to his own experience researching or studying the condition or its relationship to vaccination. In fact, even Dr. Callen's case report *conceded* that "the mechanisms of vasculitis and cryoglobulinemia induced by the influenza and pneumococcal vaccination remain unknown" and "it is not clear why cryoglobulins are produced as a response to a viral antigen triggered in response to a vaccination." Callen Case Report at 961–62.[28]

Thus, although the treater views in this case do aid Petitioner's showing, they ultimately relied too much on the obvious temporal relationship between vaccination and injury to carry Petitioner's "did cause" burden. *See, e.g.*, Callen Case Report at 962 ("Although a causal link with the influenza vaccination cannot be proved by our observation, we can speculate that based on the timing of the vaccination, constellation of symptoms, and positive laboratory results, influenza virus-induced cryoglobulinemia is the most probable cause of our patient's symptoms"). This determination is bulwarked by the unpersuasive showing Petitioner made on the first, "can cause" prong; even if I had found in this case that Petitioner had satisfied the "did cause" prong, his failure to preponderantly establish the first would still be fatal to his claim. *W.C.*, 704 F.3d at 1356.

The evidence about Dr. Temes's subsequent development of vasculitis, as diagnosed in 2017, is similarly unsupportive of the conclusion that his injuries were likely vaccine-caused. While the record preponderantly substantiates that Dr. Temes was properly diagnosed with leukocytoclastic vasculitis in 2017, it is also the case that the symptoms leading to that diagnosis did not manifest until a significant time *after* onset of his cryoglobulinemia in 2015. Tr. at 97–98; Ex. 54 at 1, 7 (documenting onset of a rash on or around May 25, 2017, and the first biopsy result confirming the rash as cutaneous vasculitis on May 30, 2017); Ex. 19 at 17 (confirming Petitioner's vasculitis diagnosis and more specifically classifying it as leukocytoclastic vasculitis in June

[28] I also note that Dr. Callen's expertise, which lies largely in dermatology further diminished the probative value of his causation observation.

2017). As a result, even if vasculitis can (at least as established in some case reports) be observed to be vaccine-caused or secondary to cryoglobulinemia,[29] here Dr. Temes's vasculitis so significantly post-dated vaccination that it is difficult to associate the October 2015 vaccines with it (especially in the absence of a credible scientific explanation for how the one-time event of vaccination resulted in a chronic and persistent condition manifesting as leukocytoclastic vasculitis over 15 months later). My conclusion is bulwarked by the fact that the case reports offered by Petitioner to support an association between vasculitis and vaccination all involve far *shorter* post-vaccination onsets. *See, e.g.*, Tavadia (onset of leukocytoclastic vasculitis within one to two weeks of receipt of the flu vaccine).

C. *Althen Prong Three*

Petitioner's showing with respect to the third *Althen* prong, involving onset timeframe, presents a similarly "mixed bag" of evidence that in the end cannot satisfy this element of his burden, largely due to his inability to persuasively establish the first prong.

The record in this case establishes an obviously close temporal association (approximately five to seven days) between the date of Dr. Temes's vaccinations and initial symptoms onset. Treaters deemed this temporal relationship significant enough to support the conclusion that the flu and/or pneumococcal vaccines were causal of Petitioner's cryoglobulinemia. But as a matter of reliable science, was that timeframe medically acceptable?

Dr. Schroeder noted that it takes approximately five to seven days from the time of vaccination for B cells to *begin* the production of plasma and memory cells. Tr. at 117. It then takes up to three to four weeks *more* for the body to produce enough IgM antibody to induce cryoglobulinemia. *Id.* at 139, 156, 158. And even in Catsoulis, the item of literature most on-point in associating vaccination with cryoglobulinemia, the process of causing appearance of the cryoglobulins took several weeks (and only after repeated vaccination). Catsoulis at 328.Thus, what is known about the pathogenesis of cryoglobulinemia cuts against such a short turn-around from vaccination to manifestation of the clinical symptoms Petitioner first reported (hand discoloration, swelling, pain, etc.).

In response, Petitioner argued that Dr. Temes would likely have experienced a faster response because he had developed immunologic memory from the flu vaccines he had received throughout his life. Tr. at 139. This proposition, however, was devoid of any literature or expert support suggesting that such memory can cause the processes resulting in cryoglobulinemia to occur faster than otherwise usual (even taking into account the fact that Petitioner received a high

[29] I do find, however, that Respondent made a robust showing rebutting this conclusion, as evidenced in Bonetto (which does not support the vaccine-vasculitis association) or Monzajeb and Fox (in which findings of post-vaccination vasculitis did not also involve cryoglobulinemia).

dose version of the vaccine). This contention was also undermined by the fact that the seasonal flu vaccine varies year to year, depending upon what strains of the virus are predicted to be most prevalent (and thus included in the current formulation). *See* Lohse at 359; Tavadia at 155. It is therefore speculative to assume that Dr. Temes would likely have had immunologic memory for the exact flu vaccine formulation he received in October 2015.

Because of the above, I cannot find that Dr. Temes's onset post-vaccination was medically acceptable, despite some treater views to the contrary.

CONCLUSION

Dr. Temes was an engaging witness, and he plainly brought this case in the good-faith belief that the vaccinations he received might be related to his subsequent and sudden development of cryoglobulinemia. The fact that those symptoms arose so close in time to vaccination was facially suspicious, and Petitioner unquestionably has marshalled credible treater support for his claim—even if that support overinvests in the significance of the temporal association between onset and vaccination (something the law does not do).

But I am compelled by the Vaccine Act and other controlling precedent to decide this case based upon a preponderant standard, and to weigh evidence offered in support of a claim based upon its scientific and medical reliability. Here, the Petitioner did not successfully establish that either the flu or pneumococcal vaccines, acting alone or in combination, could cause cryoglobulinemia, and/or do so in a timeframe of one week. Thus, the evidence in the record did not ultimately preponderate in a favorable ruling, even though Petitioner's showing on the second *Althen* prong was more robust.

Accordingly, and for the aforementioned reasons, I **DENY** entitlement in this case. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** in accordance with the terms of this Decision.[30]

IT IS SO ORDERED.

s/ Brian H. Corcoran
Brian H. Corcoran
Chief Special Master

[30] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.