In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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WALTER THORNTON,	*	
	*	No. 18-1002V
Petitioner,	*	Special Master Christian J. Moran
	*	
v.	*	
	*	Filed: September 4, 2025
SECRETARY OF HEALTH	*	
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	
* *		

William E. Cochran, Jr., Black McLaren, et al., PC, Memphis, TN, for Petitioner; Joseph Leavitt, United States Dep't of Justice, Washington, DC, for respondent.

DECISION DENYING COMPENSATION[1]

Walter Thornton alleges that a seasonal influenza vaccination administered on September 30, 2016 caused him to develop rhabdomyolysis on October 11, 2016. The Secretary disputes this claim. Mr. Thornton submitted reports from an expert in immunology, rheumatology, and internal medicine, Dr. Gershwin. The Secretary responded with reports from an expert in rheumatology, Dr. Rose, and an expert in neurology and neuromuscular disorders, Dr. Donofrio. The parties also filed briefs. A hearing was held on June 8, 2023 and October 24, 2023, during which Mr. Thornton and the parties' experts testified. Mr. Thornton has not persuasively shown that a flu vaccine can cause rhabdomyolysis, or that it can do so in the relevant time period. Accordingly, he is not entitled to compensation.

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

First, a brief explanation of rhabdomyolysis is provided. This is followed by the factual history and procedural history of the case, and an explanation of the standards of adjudication. An overview of cytokines and their relation to Mr. Thornton's theory is presented before an analysis of each Althen prong.

I. Rhabdomyolysis

Rhabdomyolysis is a lysis (rupture) of the skeletal muscles. Efstratiadis at 129.[2] "Lysis of muscle cells releases toxic intracellular components in the systemic circulation which leads to electrolyte disturbances, hypovolemia, metabolic acidosis, coagulation defects and acute renal failure due to myoglobin." Id. A person undergoing rhabdomyolysis is experiencing intracellular hypoxia, meaning that "the cell is unable to provide enough oxygen via its own respiratory function." Tr. 139 (Dr. Gershwin). When the cell is unable to function because it does not have enough oxygen, the cell dies and the cell membrane opens, pouring out myoglobin into the muscle enzyme. Tr. 72, 139. This clogs the kidneys, resulting in renal failure. Tr. 73.

Rhabdomyolysis is "characterized by acute elevation of serum creatine kinase (CK) activity, with the presence of myoglobinuria and acute kidney injury." Hamel at 622. While a severe case of rhabdomyolysis "suggests a genetic origin," viral infections as an origin are "frequently reported." Id. Rhabdomyolysis is a syndrome, and is "usually the result of multiple contributing factors," such as physical exertion, direct muscle injury, muscle ischemia, temperature extremes, drugs/toxins/venoms, metabolic or endocrinologic conditions, genetic factors, infections, or autoimmune myopathies. Efstratiadis at 129, 130 (Table 1).

II. Factual History

Mr. Thornton was born in 1989. Pet. at 1. In 2016, when he was 27 years old, Mr. Thornton was serving on active duty in the Air Force. Exhibit 4 at 4. Mr. Thornton exercised frequently; he worked out at the gym for 3-4 hours per day approximately 5 days per week, biked, and enjoyed various sports. Exhibit 16 (Affidavit, dated Oct. 2, 2018). He ran two miles and did 60 push-ups and 60 sit-ups each weekday. Exhibit 129 (Affidavit, dated Feb. 27, 2020). Mr. Thornton's medical history was significant for diarrhea and dehydration that was treated in the emergency room, a knee injury from basketball, and persistent plantar fasciitis and

[2] Bibliographic information for the articles cited in this decision is found in the appendix.

Achilles' tendinitis, which were treated with steroid injections. Exhibit 3 at 680-93, 703-09, 720-50, 768-74.

On September 12, 2016, Mr. Thornton received an inactivated polio vaccine. Exhibit 3 at 9. Three days later, he underwent a pre-deployment health assessment with Certified Nurse Practitioner Jo Schroeder at the Holloman Air Force Base. Id. at 646. Mr. Thornton's "General overall feeling / health" was reported to be "Very Good." Id. CNP Schroeder stated that Mr. Thornton was "Deployable at present, but requires medical readiness updates." Id. at 648.

Over the next few weeks, Mr. Thornton continued his regular exercise routine, running and doing push-ups and sit-ups on the weekdays. Exhibit 129 at 1. On Friday, September 30, 2016, after doing his daily exercise, Mr. Thornton received a flu vaccine. Exhibit 2 at 1. Mr. Thornton's shoulders and upper thighs were sore for the three days following his flu vaccine. Exhibit 129 at 1-2. He received an anthrax vaccine on October 3. Id. at 2.

Mr. Thornton did not exercise Saturday, October 1, through Monday, October 10, as exercise was optional on weekends; for one week following immunization; and for one week leading up to physical fitness testing (or "PT testing"). Exhibit 129 at 1-3. On October 11, he attempted his PT testing. Id. at 3. Mr. Thornton did approximately 42 sit-ups and 38 push-ups, and then collapsed during a 1.5 mile run. Id. Mr. Thornton avers:

> After about one-half mile of running, I began experiencing soreness in my upper thighs, legs, biceps, shoulders, and abdomen. At first, I thought the soreness was normal, but it got progressively worse to the point that I was experiencing excruciating pain all over my body, which forced me to collapse.

Id.

Mr. Thornton arrived at the Gerald Champion Regional Medical Center ("Champion") Emergency Room and saw Waseem Khawaja. Exhibit 4 at 35. Mr. Thornton presented with right knee injury and pain. He reported that both knees locked up and he fell while running, causing pain in his knee. Id. Mr. Thornton was diagnosed with dehydration, azotemia with doubling of creatinine, right knee injury, and elevated creatinine even after he received saline. Id. at 40. Due to the elevated creatinine, Dr. Khawaja recommended that he follow up with a kidney specialist due to rule out intrinsic kidney disease. Id.

Mr. Thornton returned to Champion the next day with a chief complaint of muscle aches. Exhibit 4 at 62. He reported that after he was discharged the day prior, "he developed significant excruciating muscle pain throughout [his] abdomen, large muscles of the upper arms, and his thigh area." Id. Mr. Thornton "was found to have acute rhabdomyolysis with myoglobin over 3781 and a CK of 178,770." Id. Despite receiving fluid treatments, Mr. Thornton continued to have worsening kidney function, and he "was found to also have acute liver injury with significant elevation in his liver function tests" since the previous day's labs, and metabolic acidosis. Id. at 59-60. His discharge diagnosis was acute rhabdomyolysis, acute kidney injury, acute liver injury, and metabolic acidosis. Id. at 59. Mr. Thornton was transferred to William Beaumont Hospital ("Beaumont") for a higher level of care. Id. at 60.

Mr. Thornton's medical history taken upon his admission to Beaumont on October 13, 2016 states that he "did a ruck march of about 20 miles, and has run approximately 40 miles in the last 2 days." Exhibit 5 at 6. However, the very next day, he denied that he had done a ruck march or run 40 miles. Id. at 276. Rather, he stated that he had been resting before the PT test where he collapsed. Id.; see also Exhibit 116.[3] Mr. Thornton was assessed as having "exertional rhabdomyolysis," although he denied overexertion and stated he had been doing his usual exercise routine. Id. at 8-9.

Mr. Thornton received aggressive fluid hydration in the Beaumont ICU. "His course in the ICU was complicated by hypertension resistant to increasing doses of labetalol/nifedipine," and his elevated blood pressure was attributed to kidney injury. Exhibit 5 at 263. He was placed on intravenous diuretic therapy.

[3] The October 13, 2016 medical record states that Mr. Thornton participated in a ruck march and 40 miles of running. As soon as the very next day, Mr. Thornton denied doing these exercises, and has consistently denied it since that point. Exhibit 116 (affidavit, dated Nov. 22, 2019); Tr. 43. The only other mention of a 40-mile run appears over a year later in a December 20, 2017 medical record, and it is possible that this doctor took this information from the October 13, 2016 record. He does not state that Mr. Thornton told him this. Exhibit 12 at 93. Mr. Thornton would have been motivated to tell the truth about his exercising while at the hospital in order to receive necessary and effective treatment. Moreover, his denials predate his claim for compensation from the Vaccine Program, undermining any concern that he was motivated to claim vaccine causation. In sum, preponderant evidence favors a finding that Mr. Thornton did not engage in a ruck march or do approximately 40 miles of running. See Tentative Findings, issued Nov. 27, 2023.

Mr. Thornton was eventually taken off maintenance fluids, Lasix, and supplemental oxygen, and was transferred to the wards. Id.

Mr. Thornton was discharged on October 22, 2016. His discharge diagnosis was:

- Exertional non-traumatic rhabdomyolysis – resolved
- Oliguric heme pigment-induced acute kidney injury/acute tubular necrosis – improved
- Abnormal liver enzymes, mostly likely due to #1, improved
- Hypertension – due to #2, improved
- Non-specific elevation in troponins – due to #1 and #2
- Abdominal pain – resolved, most likely mild acute pancreatitis

Exhibit 5 at 263. The "Hospital Course/Narrative Summary" stated that his rhabdomyolysis was "Possibly secondary to exertion," and that taking one acetaminophen per day for two weeks "may have contributed." Id. It was also noted that Mr. Thornton "ha[d] a HIGH risk of recurrence (Rhabdomyolysis after low to moderate workload AND severe kidney injury)." Id. at 264 (emphasis in original).

Mr. Thornton returned to Champion on October 27, 2016 with complaints of abdominal pain. Exhibit 4 at 21. He received a CT scan of his abdomen and pelvis, which was normal. Id. at 24. He was given fluids and felt much better, and was instructed to return to the emergency room the next day for repeat labs. Id. at 25.

On October 28, Mr. Thornton returned to Champion with nausea, but no vomiting or abdominal cramping. He felt weak but could move his arms and legs without difficulty. He noted that he had not been active whatsoever. Exhibit 4 at 11. Mr. Thornton was transferred to Beaumont again with a diagnosis of rhabdomyolysis and nausea. Id. at 14.

At Beaumont, Mr. Thornton informed his treating doctors that his pain had been worsening since his prior discharge from Beaumont. Exhibit 5 at 439. The pain was mostly in his upper thighs, glutes, and stomach, and it did not radiate. He reported weakness in his legs and shortness of breath while walking. Nothing seemed to relieve the pain, and walking worsened it. Id. He underwent various tests and was treated with high fluid hydration and intravenous Solu-Medrol (which were not successful, see Exhibit 3 at 567) and two rounds of IVIG. Id. at 623. Mr. Thornton was discharged on November 9, 2016 with diagnoses of

"Inflammatory myositis – etiology unclear", "Non-exertional, non-traumatic rhabdomyolysis", and "Essential hypertension." Id. He was to go to the neurology clinic the following day for a third round of IVIG. Id.; see also Exhibit 6 at 265-66.

Mr. Thornton was seen by neurologist Shawna Scully on November 14, 2016 for "acute followed by protracted rhabdomyolysis." Exhibit 3 at 567. Dr. Scully noted that he had recently received several vaccinations. She described "the "initial bout" as occurring "in the midst of an aggressive physical fitness training test." It then "seemed to have fully resolved" after Mr. Thornton's initial hospitalization before his weakness returned despite his resting. She also recorded that his CK levels were in the 1000s at Beaumont, and an MRI of his legs showed an inflammatory process consistent with rhabdomyolysis. Id. His CK levels improved after the IVIG treatments, and he now had "not just normal but even lower than previous results." He still complained of muscle pain and felt a sharp stabbing pain in his lower back. Dr. Scully prescribed calcium/vitamin D and magnesium. She wrote, "As best I can tell this is an autoimmune mediated process, perhaps triggered by several recent vaccinations." Id. at 573.

Mr. Thornton followed up with Dr. Scully on November 23, 2016. She again noted the vaccinations he received in the weeks before his PT test, and stated that "he typically maxes his PT tests." Exhibit 6 at 206. At the appointment, Mr. Thornton had "the best CK levels he has had to date," and was "stable and tolerating simple in-home ambulation." Id. Mr. Thornton reported profound fatigue, decreased exercise tolerance, and a degree of shortness of breath and occasional lightheadedness with exertion. Id. He also had lower back pain and muscle pain in his hips and thighs. Id. at 210. The assessment included myositis, orthostatic hypotension, and low back pain. Dr. Scully stated that once Mr. Thornton was cleared by cardiology, he could begin more advanced physical therapy with the goal of reconditioning. Id.

Cardiologist Maria Frisbie-Veal saw Mr. Thornton on December 5, 2016. Exhibit 6 at 199. Mr. Thornton complained of an intermittent "burning sensation," chest pain, dyspnea, and palpitation with exertions and at rest. Id. The exam was normal, but Dr. Frisbie-Veal requested various tests. Id. at 204.

Mr. Thornton saw Dr. Scully again on December 27, 2016. Exhibit 6 at 121. His CK levels had improved even more, but he continued to struggle with profound fatigue, decreased exercise tolerance, and a degree of shortness of breath and occasional lightheadedness with exertion. Id. at 123. Mr. Thornton expressed frustration at being unable to play with his toddler at home due to his pain. He

stated that he did not have a family history of rhabdomyolysis, muscle breakdown, atrophy of muscles, or renal failure. Id.

Dr. Scully reported that Mr. Thornton's cardiology tests were within normal limits, and stated that most of his symptoms "seem to be accounted for by profound deconditioning." Exhibit 6 at 123. He still had significant pain in the shoulder girdle, paraspinal muscles, hip girdle, gluteus, thighs, and calves. An exam of his musculoskeletal system found "Tenderness to palpation in all major muscle groups but most notably the deltoids, pan-paraspinal musculature, glutes, quads, hamstrings and calves." Id. Lab results were negative for autoimmune markers and infectious pathogens. Id. at 123-24, 130-32. In her assessment, Dr. Scully stated:

> Patient appears to have suffered from an autoimmune inflammatory myositis . . . culminating in profound rhabdomyolysis . . . at no time when he was under the care of military medical providers did he demonstrate frank evidence of renal compromise in spite of the dramatically elevated CK levels. My concern is that he [has] shown essentially no significant improvement in strength [or] exercise tolerance in spite of normalization of all labs status post administration of IVIG therapy. Tissue biopsy thus far only shows rare angular atrophic fibers with no other information that affords a more detailed differential diagnosis. To further support at this time and in an effort to salvage his military career will refer him to a neuromuscular specialist for more detailed assessment and hopefully outlining a better plan for recovery.

Id. at 144.

Mr. Thornton saw neuromuscular specialist Erik Ortega on January 27, 2017. Exhibit 7 at 1. Dr. Ortega noted that there was an initial concern that overuse resulted in rhabdomyolysis, but stated that the physical activity in the fitness test was normal to Mr. Thornton "so one would not expect that he would have rhabdomyolysis as a consequence." Id. Mr. Thornton reported no personal or family history suggestive of prior rhabdomyolysis episodes. He continued to experience headaches and a sharp, constant pain in his back, buttocks, thighs, and head. Id. at 3. Myositis Panel 1 markers were negative, and an EMG on Mr. Thornton's right thigh was unremarkable. Id. at 2-4, 43-48.

In his "Impression and Plan," Dr. Ortega reported that there was some improvement in Mr. Thornton's muscle enzyme testing, but he continued to have persistent symptoms. Exhibit 7 at 4. Dr. Ortega wrote:

> I most strongly suspect that his rhabdomyolysis was induced by his exposure to vaccinations. There are a number of case reports describing patients who have rhabdomyolysis following a variety of vaccinations . . . The difficult thing is as to why he has persistent symptoms. I do not feel that the disease that resulted in his presentation is necessarily still active given the unremarkable nature of his EMG, normal muscle enzyme testing as well as normal strength. I have met plenty of patients who have had episodes of rhabdomyolysis who [have] had long-standing muscle pain following without any active pathology revealed despite extensive testing. At this point in time I suspect he will improve but I do not feel that there is something that I am able to provide him that would necessarily expedite his improvement . . . If he has a persistently elevated [CK] that would be disproportionate for a young African-American male there may be an underlying genetic disorder contributing to his clinical picture, although it is not strongly suspected given the paucity of family history or personal history, prior to the episode, that would argue for an underlying genetic disorder.

Id. Dr. Ortega also wondered if Mr. Thornton might have central sensitization syndrome, causing allodynia and his persistent symptoms. Id. at 5. He ordered repeat muscle enzyme testing and an evaluation for myositis specific antibodies.

Mr. Thornton followed up with Dr. Scully on March 8, 2017 for myositis. Exhibit 6 at 100. He reported that his generalized muscle pain had not improved since his last visit. His legs felt more fatigued than his arms, and he had difficulty breathing deeply and focusing. He also reported a frontal recurring headache. Id. Dr. Scully described Mr. Thornton's condition as "autoimmune myositis thought to have been associated with the administration of vaccinations." Id. at 102. She stated that they "were able to resolve active rhabdomyolysis/prevent further muscle breakdown as evidenced by chronically elevated ck values with the initiation of IVIG and no recurrence since that initial therapy." However, Mr. Thornton "continued to have incapacitating muscle pain that is leading to marked decrease in exercise tolerance," and they were thus far unable to control his discomfort. Id. There was no frank weakness and no abnormality on the EMG, but the discomfort made him "significantly limited [in] functionality." His neurological exam was still normal, "aside from diffuse muscle pain even to palpitation." Id.

Because of Mr. Thornton's "new [symptoms] of pain with [extra-ocular eye movements intact (EOMI)] and pupillary light response as well as worsening [shortness of breath/ dyspnea on exertion] with a recently negative cardiac work-

up," Dr. Scully referred him for an ophthalmologist and pulmonologist consultation. Exhibit 6 at 102.

Mr. Thornton had an April 10, 2017 appointment with pulmonologist Gregory Brown. Exhibit 11 at 755. His chief complaints were intermittent dyspnea and history of myositis. He reported that since October 2016, he experienced shortness of breath when walking distances greater than 100 feet, causing him to stop and catch his breath. Id. at 756. He also reported anxiety and generalized pain in the muscles of his upper and lower extremities and lower back. His gait was abnormal due to pain. Id. Dr. Brown opined that the dyspnea might be secondary to Mr. Thornton's musculoskeletal weakness from his underlying myositis rather than from deconditioning, and did not suspect underlying bronchoreactivity. Id. at 759.

Mr. Thornton had high CK values on August 28, September 1, and September 6, 2017 (values of 498, 396, and 397 vs. a normal range of 50-196). Exhibit 3 at 89. He returned to Beaumont on September 12, 2017 because his primary care provider was concerned about these elevated levels. Exhibit 5 at 819. He also continued to experience "lifestyle affecting symptoms, particularly malaise, generalized pain, described as 'tenderness', and intermittent chest pain." He also reported a "persistent, non-productive, hacking cough for the past six months." Id. Mr. Thornton reported that he had been taking prednisone daily through April, at which point his doctor told him to take it only as needed. Since then he had taken it twice per week at most. On September 6, he was prescribed prednisone 5 times per day but had not taken it as of his September 12 appointment. Id. at 821. Mr. Thornton was admitted to the medicine ward for IV steroids and fluids. Id. at 821-22. The doctor at Beaumont "Suspect[ed] recurrent autoimmune inflammatory myositis," and stated he could be discharged after three days of IV treatment if his CK levels stabilized. Id. at 839. After treatment, Mr. Thornton was discharged on September 15, 2017 in hemodynamically stable condition. Id. at 892.

On October 4, 2017, Mr. Thornton was "medically separated from the military as his condition [made] him currently not employable." Exhibit 9. It was further noted that his "prognosis is yet unclear at this point as he continues to be actively evaluated and treated by neurology." Id.

Mr. Thornton saw rheumatologist fellow Ashley Blaske on April 2, 2018. Exhibit 12 at 30. Dr. Blaske stated that Mr. Thornton had a second episode of rhabdomyolysis in September 2017 after working out. Id. at 31. Mr. Thornton had been advised "not to exercise or even walk long distances" for fear of triggering

another episode. He used to be very active with no prior episodes. He currently occasionally swam and did not lift weights, and reported abdominal pain after minimal activity. He denied muscle weakness. Id. A physical exam was normal, and Mr. Thornton had negative ANA and normal CBC and CMP. Id. at 33. Dr. Blaske suspected metabolic myopathy, noting that it was "A little unusual to present later in life, but myalgias without weakness and elevated CK are classic for metabolic myopathy." She saw "no evidence of inflammatory or autoimmune myositis like polymyositis." Id.

At a physical therapy assessment on February 19, 2019, Mr. Thornton complained of an inflammatory condition and pain in his back, buttocks, both feet, and abdomen. Exhibit 115 at 40. He stated that he had been using crutches recently to steady himself, because his body "gives out easily." Id. His legs had been buckling since October 2016, and he had last fallen about a month ago. Id. at 40-41. The assessment was chronic musculoskeletal pain in the low back, thighs, and buttocks. Id. at 38. Mr. Thornton attended physical therapy five times between September and November 2019. Exhibit 128 at 16-36.

Mr. Thornton still experienced chronic pain in his back and bilateral thighs on January 9, 2020. Exhibit 128 at 12. On December 28, 2020, he was assessed as having chronic musculoskeletal pain/history of myositis/lumbar spondylosis/bilateral plantar fasciitis" and "History of rhabdomyolysis 2016: Asymptomatic." Exhibit 162 at 20. This was the final medical record filed.

III. Procedural History

Represented by Attorney William Cochran, Jr., Mr. Thornton initiated this case by filing his petition on July 12, 2018, alleging that the polio vaccine and flu vaccine caused him to suffer from rhabdomyolysis, myositis, and autoimmune induced inflammatory myopathy. Mr. Thornton submitted medical records periodically.

A. Dr. Gershwin's First Report

Mr. Thornton retained a rheumatologist, M. Eric Gershwin, and filed his first report on April 18, 2019, along with a motion for summary judgment. Dr. Gershwin opined that Mr. Thornton suffered from an autoimmune-induced inflammatory myopathy. He explained that "Idiopathic inflammatory myopathies (immune-mediated myopathies), collectively known as myositis, are heterogeneous disorders characterized by muscle weakness and muscle inflammation." Exhibit

17 at 3. As Dr. Gershwin described, "Our theory is that [the polio vaccine] and/or flu vaccine caused his myopathy via molecular mimicry." Id. at 7. Dr. Gershwin argued that the onset of Mr. Thornton's autoimmune muscle disease occurred within an acceptable timeframe, as the literature he cited "noted that more than 50% of cases occur within three months of an environmental response." Id. Dr. Gershwin also opined that the "additional feature of exercise" in this case "may [have skewed] his cytokine response and accelerate[d] his condition." Id.

Dr. Gershwin emphasized "there were no other environmental factors that occurred prior to the onset of myositis other than the vaccinations given to Mr. Thornton. In other words, there was no clear antecedent viral infection." Exhibit 17 at 10. Dr. Gershwin further highlighted the fact that Mr. Thornton was undergoing intense exercise. "Exercise has a profound effect on the immune system, may accelerate immune response and lead to a further inability to distinguish self from non-self," he explained. Id. at 11. He opined that, more likely than not, the exercise had "a significant biologic effect above and beyond an individual that was at rest." Id.

Finally, Dr. Gershwin noted that two of Mr. Thornton's treating physicians had proposed a link between his injury and the vaccine. Exhibit 17 at 12 (citing Exhibit 7 at 1-5 (Dr. Ortega); Exhibit 6 at 99-102 and Exhibit 8 (Dr. Scully)). Dr. Gershwin ruled out other causes, as Mr. Thornton had no pre-existing or co-existing infections, and anthrax vaccines "are relatively poor immunogens and while a role for this vaccine cannot be eliminated, they are less likely to be significantly antigenic than the IPV and influenza vaccine." Id.

B. Dr. Rose's Report and Dr. Donofrio's First Report

The Secretary filed an expert report from rheumatologist Carlos Rose on July 10, 2019, and an expert report from neurologist Peter Donofrio on August 5, 2019. Exhibits A and C. Dr. Rose commented on the different diagnoses Mr. Thornton received. Dr. Rose disputed the diagnosis of idiopathic inflammatory myopathy ("IIM"), submitting that it is "exceedingly rare" to have IIM with associated rhabdomyolysis. Exhibit A at 16-17. Additionally, the absence of objective muscle weakness weighed against a diagnosis of IIM, as "weakness is the backbone of disease diagnosis." Id. at 17. Dr. Rose discussed the "classical diagnostic criteria" put forth in the Bohan & Peters paper, which listed rhabdomyolysis as an exclusionary criteria. Id. He also used the new EULAR/ACR 2017 criteria to calculate a probability of 3% that Mr. Thornton had IIM. Id. at 18-19. Dr. Rose further noted the negative muscle biopsy, normal

EMG, and the lack of response to corticosteroids as factors weighing against IIM. Id. at 19-20.

Based on the medical records and symptoms, Dr. Rose opined that "the post-rhabdomyolysis symptoms are the result of a chronic pain/amplified pain syndrome . . . rather than ongoing, persistent inflammatory myopathy." Exhibit A at 15. "In other words, what we seem to have here is an episode of acute exertional rhabdomyolysis with a milder relapse days later and the development of a chronic pain syndrome mimicking persistent muscle disease." Id.

Arguing that Mr. Thornton had exertional rhabdomyolysis rather than IIM, Dr. Rose stated that the vaccination would not have contributed to his injury, "since the primary mechanism offer[ed] is not immunologic or even inflammatory." Exhibit A at 21. In sum, he stated that Mr. Thornton did not have IIM, and that his rhabdomyolysis "was not the result of vaccination but of exertion with possible additional predisposing factor(s) yet to be determined." Id. at 22.

Dr. Donofrio's impression was that Mr. Thornton had exertional rhabdomyolysis and myoglobinuria. Exhibit C at 6. He disputed Dr. Gershwin's diagnosis of IIM, noting that Mr. Thornton did not have muscle weakness, an abnormal EMG, or abnormal muscle biopsy. Id. at 7. Furthermore, Mr. Thornton's CK level was 450 times the upper limit of normal, which would exclude an IIM. Like Dr. Rose, Dr. Donofrio discussed the Bohan & Peters diagnostic criteria and stated that Mr. Thornton would only have met one of five criteria. Id. Dr. Donofrio noted the report that Mr. Thornton did a ruck run. Id. at 8. In conclusion, Dr. Donofrio opined that "more likely than not, the petitioner's rhabdomyolysis and myoglobinuria was not the result of the vaccinations from the influenza virus and the polio virus," but rather was more consistent with a post-exertional presentation. Id.

With Dr. Donofrio's report, the Secretary also filed his Rule 4(c) Report and response to the motion for summary judgment. The Secretary took the position that summary judgment should be denied and the case should be dismissed, arguing that the proper diagnosis was exertional rhabdomyolysis and that Mr. Thornton had not met his burden under the Althen prongs.

Mr. Thornton's motion for summary judgment was denied, as the Vaccine Rules do not authorize factfinding on summary judgment, and it was not yet determined whether Mr. Thornton suffered from myositis or exertional rhabdomyolysis. Order, issued Aug. 21, 2019.

C. Dr. Gershwin's Supplemental Reports

The parties continued to file expert reports over the next year. Dr. Gershwin now agreed that Mr. Thornton most likely had rhabdomyolysis, but argued that it was a result of the combination of the vaccination with rigorous exercise. He argued that exertional rhabdomyolysis "is a self-limiting process," and that if the injury was entirely due to exercise, the muscle enzymes would have been expected to return to normal long before their elevation again in August 2017. Exhibit 117 at 3.

Dr. Gershwin further explained the mechanism of exertional rhabdomyolysis. He stated that it is due to an inflammatory response and particularly proinflammatory cytokines, as well as several co-factors such as hot environments, electrolyte imbalance, male predominance, nutritional issues, dietary supplement, alcohol, drugs, and genetic factors. It has also been associated with the flu infection. Id. Dr. Gershwin theorized that the flu vaccine "led to a rise in cytokines and that these cytokines were pro-inflammatory and exacerbated the ongoing myositis." Id. at 4. He explained that a cytokine response after flu vaccination is normal and would persist for several days, and that the cytokine release "would still have been present at the time of the PT." Id. Dr. Gershwin clarified, "Importantly, I am not offering the opinion that Mr. Thornton's cytokine response was any more intense than anyone else's. However given the inflammatory nature of pro-inflammatory cytokines superimposed on exercise, Mr. Thornton proceeded to develop this long and difficult course with muscle destruction." Id. Noting that Mr. Thornton had previously done rigorous exercise without muscle injury, Dr. Gershwin opined that "were it not for the vaccination Mr. Thornton would not have developed rhabdomyolysis." Id.

Given Dr. Gershwin's apparent change in opinion on diagnosis (IIM to rhabdomyolysis) and the change in his medial theory, Mr. Thornton was ordered to have Dr. Gershwin provide a supplemental report explaining the change in diagnosis and addressing timing in light of the new medical theory. Order, issued Dec. 16, 2019.

In a report dated March 27, 2020, Dr. Gershwin explained that he initially stated that Mr. Thornton had IIM due to his history of intense exercise without rhabdomyolysis; the severity of the rhabdomyolysis; his physicians' beliefs that he had an autoimmune polymyositis; his elevated CK levels 6 months later; and his continued pain three years later. Exhibit 130 at 1-2. He further explained that, when he wrote the first report, he "did not have the data from the Tampa VA and was unaware that [Mr. Thornton] is now in complete remission." Id. at 2. He

stated, "I do not believe he suffered from an autoimmune muscle disease because I do not believe he would now be in a period of sustained remission." Id. He maintained that a pro-inflammatory cytokine response from the flu vaccine, in combination with intense exercise and possibly subsequent cytokine release from the anthrax vaccine, caused his rhabdomyolysis. Id. at 3.

Attached to this report was a PowerPoint presentation summarizing Dr. Gershwin's theory. Exhibit 131. He showed charts from the Talaat paper (discussed later) showing that individuals vary in their cytokine release in response to vaccinations. Id. at 3. Dr. Gershwin also highlighted an excerpt from the Hervé article (discussed later) stating that "the mediators and products of inflammation at a localized site in the body may spill into the circulation and can affect other body systems causing systemic side-effects." Id. at 4. Next, he noted that exercise can cause a stronger immune response and release of cytokines. Id. at 5. He characterized the flu vaccination as "pivotal" to Mr. Thornton's injury given his regular workout regimen. Id. at 6-7.

D. Dr. Donofrio's Second Report

The Secretary did not file any more reports from Dr. Rose, but submitted a response from Dr. Donofrio. Exhibit E. Dr. Donofrio again reviewed the medical records from October 11 and 12, 2016. He argued that these records "failed to identify features of cytokine release" as described in the literature, apart from muscle pain and an elevated heart rate. Id. at 5. Although Mr. Thornton displayed those two symptoms, Dr. Donofrio noted the lack of fever, fatigue, loss of appetite, joint pain, nausea, vomiting, diarrhea, rashes, rapid breathing low blood pressure, seizures, headache, confusion, delirium, hallucinations, tremor, or loss of coordination—all of which would be signs of cytokine release. Id.

Dr. Donofrio further opined that, based on articles cited by Dr. Gershwin, Mr. Thornton's cytokine release from the flu vaccination on September 30 would have risen, peaked, and returned to baseline by the next day. Exhibit E at 5. He also commented that several case reports provided by Dr. Gershwin discussed patients who had rhabdomyolysis in the context of statins, which Mr. Thornton was not taking. Id.

Dr. Donofrio pointed out that, if Mr. Thornton's rhabdomyolysis was a pro-inflammatory condition induced by the vaccination in combination with exercise, there would likely be evidence for inflammation in the muscle. However, a biopsy of the thigh muscle did not show findings of inflammation or rhabdomyolysis. Id. at 5-6 (citing Exhibit 7 at 12-13). Dr. Donofrio again noted the report of a ruck

march in the days prior to the onset of rhabdomyolysis. Id. at 6. He repeated his diagnosis that Mr. Thornton had exertional rhabdomyolysis and myoglobinuria, and opined that he may have an underlying metabolic myopathy. Id.

E. Dr. Gershwin and Dr. Donofrio's Final Reports

In response, Dr. Gershwin submitted another report. Exhibit 156. He disputed that Mr. Thornton had done the ruck march, citing to medical histories and affidavits that countered this report. He also clarified that he did not think that there was a cytokine storm. Dr. Gershwin disputed the suggestion that Mr. Thornton had a metabolic myopathy, and noted that although Dr. Ortega had mentioned the possibility, none of the later treaters felt compelled to test him for such. Id. at 1. Regarding the muscle biopsy, he was not dissuaded, noting that it "did not even show the working diagnosis of the government experts, rhabdomyolysis." Id. at 2.

The final report was submitted by Dr. Donofrio. Exhibit F. He reiterated that there were records noting that a ruck march had taken place. He also maintained that there was evidence of a metabolic myopathy: exertional pain, elevated CK, and a normal exam. "The fact that none of the subsequent treating physicians pursued genetic testing for a metabolic myopathy also does not imply the testing was not necessary." Id. at 1.

F. Procedural History Following Expert Reports

An order for briefs issued on November 12, 2020. Mr. Thornton filed his brief on March 18, 2021. The Secretary submitted his brief on July 16, 2021, and Mr. Thornton replied on September 8, 2021.

Due to the dispute over whether Mr. Thornton participated in a ruck march around October 11, 2016, the parties were directed to seek additional information regarding Mr. Thornton's military training. Order, issued Oct. 20, 2021. In a memo dated December 16, 2021, a staff judge advocate for Holloman Air Force Base stated that the squadron did "not possess any responsive documents." Court Exhibit 1001.

After it was determined that the case would go to a hearing, the parties were ordered to file supplemental briefs regarding pain and suffering. Order, issued Feb. 22, 2023. Mr. Thornton submitted a brief on March 24, 2023, and the Secretary submitted a brief on May 2, 2023.

A hearing was scheduled for June 6 and 7, 2023. Order, issued April 12, 2023. Mr. Thornton and Dr. Gershwin testified on June 6, and Dr. Rose began his testimony. However, the second day was rescheduled due to illness. See Order, issued June 8, 2023. The hearing was completed on October 24, 2023 with testimony from Dr. Rose, Dr. Donofrio, and Dr. Gershwin.

Following the hearing, the undersigned made two tentative findings: that Mr. Thornton did not participate in a ruck march, and that Mr. Thornton did not suffer from a metabolic myopathy. Order, issued Nov. 27, 2023. The parties were ordered to file post-hearing briefs. Although the parties could raise any issue in the briefs, they were instructed to address the reliability of Dr. Gershwin's opinion that elevated cytokines could continue to affect a person through signaling after returning to normal. Id.

Mr. Thornton submitted his post-hearing brief on January 29, 2024. The Secretary responded on March 28, 2024, and Mr. Thornton replied on April 24, 2024. With the submission of these briefs, the case is ready for adjudication.

IV. Standards for Adjudication

A petitioner is required to establish his case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "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 v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Hum. Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

When pursuing an off-Table injury, a petitioner bears a burden "to show by preponderant evidence that the vaccination brought about [the vaccinee's] injury by providing: (1) a medical theory causally connecting the vaccination and the

injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

V. Cytokines

Cytokines are signaling molecules. Dr. Gershwin explained that cytokines are measured during vaccine development to gauge the vaccine's efficacy, as an activated immune system leads to an increase in cytokine production. Tr. 74-75. When people suffer from rhabdomyolysis, the cytokines signal the cells abnormally, which results in an increase in calcium and ultimately leads to the lysis of the cell membrane and hypoxia. Tr. 137.

Cytokines play a key role in Mr. Thornton's theory, both in causation and in timing. He argues that the cytokines released by the flu vaccine and exercise can cause rhabdomyolysis. Relatedly, he argues that the cytokines from the flu vaccine can continue to affect the body for such a period of time that the effects were still lingering when Mr. Thornton exercised, resulting in his rhabdomyolysis eleven days post-vaccination. Therefore, a discussion of cytokines is helpful to understand the parties' arguments. First, the relationship between cytokines, exercise, and rhabdomyolysis is summarized. Next, there is an overview of the evidence regarding cytokine elevations, followed by a section on the effects of the cytokines even after they have returned to their baseline levels.

A. Cytokines, Rhabdomyolysis, and Exercise

Cytokines are released following exercise. Tr. 84 (Dr. Gershwin); Edwards & Booy. Exercise "changes the immune response" and also promotes the immune response to vaccination. Tr. 84-86. "Chronic exercise or high levels of physical activity have been shown to be related to improved vaccination responses in older adults, illustrating improved immune function." Edwards & Booy at 907. "Even a single acute bout of exercise is well known to elicit significant changes in the immune system . . . Related to these changes are the well-known leukocytosis response, and a transient increase in cytokines." Id. at 908.

It is undisputed that exercise can induce rhabdomyolysis, although there is not a consensus as to the mechanism by which this occurs. The Kim paper cited by Dr. Gershwin states that "the underlying mechanisms of [exertional rhabdomyolysis] have not been clearly established among health professionals or

sports medicine personnel." Kim at 324. The authors note that calcium "has been suggested as an important factor in the pathogenesis" of exertional rhabdomyolysis, explaining that calcium increases during exercise through cell activation and muscle contraction, and that "an increase in [calcium] in the cells may induce [exertional rhabdomyolysis] by creating energy, while controlling the cell signaling pathway system through interactions that may cause cell death." Id. at 324-26. The authors then identified primary factors associated with exertional rhabdomyolysis such as exercise experience, level of physical fitness, and intensity, duration, and type of exercise. Id. at 326. Secondary factors included hot environments, electrolyte imbalance, sex, nutritional problems, creatinine supplements and alcohol, various diseases such as viral infections, and genetic deficiency of metabolic factors. Id. at 327-28. In their conclusion, the authors stated that "Further studies on the mechanism of [exertional rhabdomyolysis] are warranted to establish prudent or better guidelines to prevent future cases." Id. at 330.

The Hamel article states that febrile illness or exercise frequently precipitate rhabdomyolysis, and that both are associated with "elevated temperature and high circulating levels of pro-inflammatory mediators such as cytokines and chemokines." Hamel at 620. The authors note the possibility that pro-inflammatory cytokines "may lead to metabolic compensation and rhabdomyolysis." Id. They conclude that the information they reviewed "increasingly points to a link between rhabdomyolysis and inflammation." Id. at 626.

In his second expert report, Dr. Gershwin described the mechanism of exertional rhabdomyolysis:

> The mechanism of exercise-induced rhabdomyolysis is due to an inflammatory response and particularly proinflammatory cytokines. There are a number of co-factors which have already been identified, including hot environments, electrolyte imbalance, male predominance, nutritional issues, dietary supplements, alcohol and genetic factors and use of drugs. It is noted that alcohol aggravates muscle damage by innate immune reactions influenced by inflammatory cells. Interestingly, exertional rhabdomyolysis has been associated with influenza infection.

Exhibit 117 at 3 (internal citations omitted).

Dr. Donofrio testified that the question over the mechanism of exercise-induced rhabdomyolysis has not been "fully resolved." Tr. 207. He stated:

> I know some people think it is due to ischemia of muscle from exercise, and then that ischemia interferes with the sodium, potassium, and chloride channels. And when sodium rushes into a cell and potassium rushes out and calcium rushes out, then you have a breakdown of the [sarcolemma]. The [sarcolemma] is the wall of the muscle that surrounds the cytoplasm, and then you get breakdown of that. You get a release of CK, which is an internal muscle enzyme. Another one that isn't talked about much is aldolase. And then if there's enough breakdown of muscle, you go into rhabdo, and then you run into the possibility of renal failure because myoglobin is toxic to the kidney.

Id.

Dr. Rose stated:

> The recognized mechanism for exertional rhabdomyolysis is interference with the availability of energy sources in the muscle cell that's [Adenosine Triphosphate (ATP)], which in reality becomes phosphocreatine thanks to reaction of the [CK], which is a way the muscle retains energy. So if this imbalance between the demand and the available energy source is what induces the electrolyte changes, ATP is necessary for the pumps to maintain the electrolyte homeostasis between the intra and extracellular. And I don't want to exaggerate in here. I'm not an expert in rhabdomyolysis, but my understanding is it's sort of an imbalance between the available energy and the demand, which eventually leads to disruption of the cell membrane and the leakage of all these biochemical markers that we find in rhabdomyolysis. There is no question in my mind that when you have this amount of myoglobin and other factors in the circulation, that your cytokine mechanism will be activated if not at least to – called the cleaner – the cleanup crew, which is the macrophages, to take the debris out of the system, and those do respond to cytokine signals. Cytokines are released for – in our body for a lot of reasons. So I do not doubt that once rhabdomyolysis is triggered that the cytokine would have a role without any doubt. I don't know about measurements of cytokines during or right before or different stages of the episode of rhabdomyolysis, but I would not doubt asserting that cytokines have a role at least in the post-rhabdo event.

Tr. 274-75. Dr. Rose did not think he could answer the question of whether cytokines were involved in the *initiation* of exertional rhabdomyolysis, but

"suspect[ed] not based on the fact that [he] see[s] a lot of cytokine release syndromes without rhabdomyolysis." Tr. 277.

In short, there is a lack of knowledge as to why rhabdomyolysis develops. Some evidence, such as the Kim article, Dr. Donofrio's testimony, and Dr. Rose's testimony, tends to point to a problem in chemistry, such as calcium. Other evidence, such as the Hamal article and Dr. Gershwin's testimony, point to a problem in inflammation, including cytokines.

B. Duration of Cytokine Elevation and Effects

After vaccination, cytokines typically rise within 12 to 24 hours. Dr. Gershwin testified that, usually, cytokines peak at 24 hours post vaccination, and they return to baseline at about 48 hours. Tr. 92, 138. The Secretary's experts likewise testified that cytokine elevation occurs within the first day after a vaccination, peaks at about 24 hours, and abates by the end of the second day. Tr. 169, 208. Dr. Donofrio stated that "the elevations [of cytokines] occur within the first day and abate by the end of the second day." Tr. 169.

Beyond the elevation of the cytokines themselves, the effects of cytokines continue after the levels return to baseline. Dr. Gershwin explained that cytokines start a signaling process, which then continues on its own without needing the cytokines. Tr. 138. He stated, "Cytokines are a biologic molecule. They're signal activators. They start signaling processes. The effects don't stop just because the level you measure that day [has] decreased. If that was true, you wouldn't see the peak of antibody responses . . . two to six weeks later after a vaccination. It's a continued effect." Tr. 288.

Dr. Gershwin cited the Hervé article to expand on this topic. The Hervé article discusses "vaccine reactogenicity," which "represents the physical manifestation of the inflammatory response to vaccination." Hervé at 1. This includes symptoms at the site of vaccination as well as systemic symptoms. Id. Reactogenicity occurs because:

> Once stimulated, the immune system sets off a complex series of innate immune events that can include phagocytosis, release of inflammatory mediators including chemokines and cytokines, activation of complement, and cellular recruitment. These phenomena are crucial for triggering strong antigen-specific acquired immune responses necessary for protection against disease. These same inflammatory events may also lead to the development

> of signs and symptoms of injection-site inflammation (pain, redness, and swelling) in the vaccinated individual. Mediators and products of inflammation in the circulation can affect other body systems to cause system side-effects (such as fever, fatigue, and headache).

Id. at 7-8. The systemic symptoms occur because "[the] mediators and products of inflammation at a localised site in the body may spill into the circulation and can affect other body systems." Id. at 14. "The main step in the development of systemic symptoms after vaccination is thought to be the presence of inflammatory markers in the bloodstream, which signal at the blood-brain barrier level and induce influenza-like symptoms." Id. at 15.

Hervé notes that there is growing evidence of an association between systemic inflammatory mediators and systemic symptoms post-vaccination. Hervé at 19. "However, no single biomarker of systemic reactogenicity has been identified, but rather a composite of biomarkers; in particular, IL-6, CRP, and for highly immunogenic products, the IFN-signalling pathway, appear to be linked to systemic reactogenicity." Id. "To date, it is unknown whether the specific molecular pathways that cause symptoms are independent from pathways involved in the generation of antigen-specific response." Id.

Hervé does not specify the typical range for these systemic symptoms to occur, stating only that they occur "soon after vaccination" or "early after vaccination." Hervé at 2. The article discusses studies detecting cytokine elevation "within hours and days after vaccination," and notes that "All of the clinical studies consistently described a slight and short-lived increase in inflammatory mediators in blood following vaccination." Id. at 15-17.

Thus, there are two components to the duration of cytokine effects: the elevation of the cytokines, and the downstream effects of the cytokines. As to the first aspect, Mr. Thornton contends that some cytokines in some individuals might remain upregulated for longer. For example, Dr. Gershwin cites Talaat to support his contention that some individuals vary "wildly." Exhibit 131 at 3. The Talaat researchers assessed the cytokines in twenty adults who received the trivalent influenza vaccine. Measurements were taken in intervals from 3 hours to 14 days, and antibody titers were measured at baseline and at 14 days. Talaat at 202. While all subjects' cytokine levels rose, the researchers observed "considerable individual variation," with one subject in particular showing a more dramatic spike and experiencing a rise and decline at a different rate within the overall cycle. Id. at 207 (Figure 3), 209.

The exception to this was the level of the cytokine IL-8. The Talaat researchers found that the levels of IL-8 in participants were reduced 44 hours post-vaccination, and remained at a low level for up to 14 days. Talaat at 207. This finding was consistent with previous findings from a larger independent cohort, and with a different research team's study on non-pregnant women. Id. at 209. Mr. Thornton contends that this demonstrates that changes in cytokine levels may be sustained for as long as two weeks post-vaccination. Pet'r's Posthear'g Br. at 11.

The Talaat article also contemplates systemic cytokine effects. The authors posit that their findings of variation in cytokine responses among individuals "support a growing body of literature indicating that soluble markers of inflammation may serve as a much-needed early indicator of vaccine reactogenicity and the risk for adverse events." Talaat at 209.

The Secretary argues that Talaat is "unpersuasive in relation to petitioner's theory of causation," as the article demonstrates a *reduction* in proinflammatory cytokines whereas Dr. Gershwin opines that an *increase* in proinflammatory cytokines caused Mr. Thornton's rhabdomyolysis. Resp't's Prehear'g Br. at 21. The Secretary notes that nothing in the article suggests that proinflammatory cytokines remained elevated up to two weeks. Resp't's Posthear'g Br. at 11. Dr. Donofrio observed that the data presented in Talaat is what would be "expected from a successful vaccination: to elicit a limited immune response against the microorganism that will lead to protection when the individual is later exposed to this pathogen." Exhibit E at 3.

Dr. Gershwin also proffered the Cohen article to demonstrate that vaccination can cause cytokine release lasting almost two weeks. Pet'r's Posthear'g Reply at 12. In Cohen, the researchers compared the cytokine responses of first-time recipients of the smallpox vaccine to the cytokine responses of revaccinees over two weeks. They found that different cytokines peaked at different rates, with different types peaking at 6-7 days, 8-9 days, 10-11, and 12-13 days after vaccination. Primary vaccinees also had higher peak levels of certain cytokines post-vaccination than did revaccinees. These levels parallelled increases in symptoms such as fatigue, lymphadenopathy, and headache. Primary vaccinees were significantly more likely to have these symptoms and experienced them for a longer duration than revaccinees. Cohen at 1183, 1186-87.

The Secretary questions the relevance of Cohen given that it involves the smallpox vaccine. Resp't's Prehear'g Br. at 39 n.28. Further, he observes that "the timeline of symptoms and side-effects that resulted from the cytokine response mirrored the rise, peak, and fall of serum cytokine levels in the subjects' blood," and thus argues that the article does not support the argument that the cytokine effects persist after the cytokine levels return to baseline, nor does it suggest that participants continued to experience symptoms after their cytokines returned to baseline. Resp't's Posthear'g Br. at 11.

In Dr. Gershwin's theory, cytokines from the flu vaccine, in combination with cytokines from exercise, can cause rhabdomyolysis. Additionally, Dr. Gershwin theorized that, between the potential for a prolonged and/or heightened elevation of cytokines in certain individuals and the lingering effects of cytokines after they return to baseline, the flu vaccine could contribute to the onset of rhabdomyolysis nearly two weeks post-vaccination.

The analysis of this theory begins with the first Althen prong, examining whether there is sound and reliable evidence that the flu vaccine is capable of inducing rhabdomyolysis. An analysis of the third Althen prong follows, discussing whether the evidence establishes that the cytokines from a flu vaccine may continue to impact the body for an extended period of time.

VI. Althen Prong One

The first Althen prong requires a petitioner to present a reliable and persuasive medical theory. Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019) (citing Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548 (Fed. Cir. 1994)).

Mr. Thornton sums up his theory in his post-hearing brief: "Petitioner's theory is that his rhabdomyolysis was caused by a proinflammatory cytokine response to the flu vaccine in combination with his intense exercise." Pet'r's Posthear'g Br. at 14. Dr. Gershwin testified that the flu vaccine predominantly produces proinflammatory cytokines. Tr. 83-84. Prostaglandins, which "are also important in the generation of rhabdomyolysis," would also be produced. Id. at 84. As discussed in Section V.A., exercise changes one's immune response and enhances the release of cytokines. Tr. 84. It also promotes the immune response to vaccination. Tr. 86. Dr. Gershwin described an underlying, asymptomatic

level of inflammation in the muscles from the flu vaccine, possibly in combination with the anthrax vaccine.[4] Dr. Gershwin did not "believe that an influenza vaccine can directly produce, by itself, hypoxia," and described hypoxia as a "secondary effect." Tr. 139-40. Rather, he theorized that the vaccine produces an underlying level of inflammation of the muscle. Rhabdomyolysis manifested when this undercurrent was combined with inflammation from exercise. Tr. 140-41.

It is undisputed that cytokines are released following flu vaccination, and that cytokines may be released following exercise. See Resp't's Posthear'g Br. at 8-9; see also Exhibit 111 (Simpson). "Given the ubiquitous nature of cytokines in the body, it cannot be enough to simply say 'cytokines did it.'" Rupert v. Sec'y of Health & Hum. Servs., No. 15-841V, 2021 WL 1832909, at *40 (Fed. Cl. May 1, 2021). "Program claimants frequently invoke the concept of vaccine-triggered cytokine production in an attempt to explain how a particular vaccine could cause a certain illness or injury. However . . . the idea that vaccines stimulate cytokine production, while scientifically correct by itself, amounts to nothing more than an explanation of how vaccines generally are expected to function. It does not explain how the initial innate response becomes pathologic." L.M. by & through McClellan v. Sec'y of Health & Hum. Servs., No. 14-714V, 2019 WL 4072130, at *27 (Fed. Cl. July 23, 2019) (citing cases).

That both the flu vaccine and exercise promote the production of cytokines does not establish that they also both play a role in the occurrence of rhabdomyolysis. Although he states that proinflammatory cytokines are generated by the flu vaccine, Dr. Gershwin does not identify the specific cytokines elevated, nor does he state whether these are the same cytokines which may induce rhabdomyolysis. See Kaltenmark v. Sec'y of Health & Hum. Servs., No. 17-

[4] Although Dr. Gershwin theorizes that the anthrax vaccine played a role in the development of Mr. Thornton's rhabdomyolysis, neither party developed meaningful arguments or submitted evidence about whether or how the anthrax vaccine may have contributed to his injury. Dr. Gershwin also noted that "Anthrax vaccines are relatively pure immunogens," and that it does not always generate an immune response. Exhibit 17 at 12; Tr. 97. Nonetheless, he did not rule out that the anthrax vaccine played an "additional role" by generating cytokines. Id. However, with no evidence about a potential link between the Anthrax vaccine and rhabdomyolysis has been provided.

1362V, 2023 WL 8870299, at *31 (Fed. Cl. Spec. Mstr. Nov. 27, 2023) (discussing the importance of distinguishing between cytokines, particularly when relying upon studies identifying specific cytokines); see also id. at *31 n.32. Likewise, while the Hamel and Kim articles (discussed in Section V.A) contemplate a link between rhabdomyolysis and cytokines, they do not discuss how a vaccine may contribute. Thus, there remains a gap in the theory between the flu vaccine and rhabdomyolysis.

To bolster his theory that the flu vaccine can cause cytokine activity which induces rhabdomyolysis, Dr. Gershwin cites a review article concluding that rhabdomyolysis is a rare complication of the flu infection and is most commonly seen in children. Kalil & Thomas at 5. Dr. Gershwin also cites to two case reports (Sevketoglu and Keverline) suggesting a link between a flu infection and exercise-induced rhabdomyolysis. The Secretary notes that the authors "did not describe how" the infection plus exercise may have triggered rhabdomyolysis in the first case, and that the patient in the second case was still advised to get the flu vaccine for future prevention. Resp't's Prehear'g Br. at 25. Moreover, the Secretary questioned whether a flu infection is synonymous with a vaccination. As the Secretary noted, the flu infection and flu vaccine are not synonymous, and the comparison does not carry petitioner's burden. See Zamora v. Sec'y of Health & Hum. Servs., No. 21-1414V, 2025 WL 1105282, at *6 (Fed. Cl. Mar. 19, 2025) (citing cases); aff'd, 2025 WL 2414590, at *4 (Fed. Cl. May 28, 2025) (distinguishing between a flu infection and flu vaccine).

Dr. Gershwin also provided several case reports discussing instances of rhabdomyolysis after vaccinations, and again noted that vaccines activate the immune system and that influenza infection is a risk for rhabdomyolysis. Exhibit 131 at 9-11.

Exhibit Numbers	**Lead Author Last Name**	**Vaccine**	**Other identified potential factors**
123, 139	Hamarat	Flu	Fibrate therapy
122, 141	Callado	H1N1	Statins
124, 142	Plotkin	Flu	Cerivastatin and bezafibrate use
125, 144	Raman	Flu	Statins

145	Chen	Flu	Statins
146	Siriwardana	Flu	Statins and cyclosporine therapy
147	Yorulmaz	Flu	Fibrate therapy
148	Shah	Flu	Simvastatin
143	Cheng	Flu	None
140	Musso	Flu	None
149	Kulkarni	Tdap	None
150	Hursitoglu	Tetanus	None

Dr. Gershwin stated that these case reports demonstrate vaccinations causing rhabdomyolysis "in combination with other factors." Tr. 80. The rhabdomyolysis would be driven by cytokines from the vaccine "plus" something else, such as drugs or exercise. Tr. 80-81. He stated that there were "several moving parts that interact" under his theory. Tr. 99. Mr. Thornton argues that "undisputed evidence supports the proposition that vaccination may act independently, or synergistically with other risk factors, to cause rhabdomyolysis." Pet'r's Prehear'g Reply Br. at 6.

The Secretary challenges the probative value of these reports, noting that many are "difficult to analogize with this case" since they involved factors such as statin and fibrate medications. Resp't's Prehear'g Br. at 26-30. Dr. Donofrio noted this as well, and affirmed that there is a "clinically accepted connection between" statin and fibrate medications and rhabdomyolysis. Tr. 167-68.

Dr. Donofrio described case reports as "simply, in most cases, the report of one patient experiencing a disorder that is thought to relate to factors in the history and physical." Tr. 167. Dr. Donofrio appeared to question the relevance of these case reports as most of the subjects were taking statins when they received their vaccinations, and Mr. Thornton was not taking statins. Tr. 167-68; Exhibit E at 5. Dr. Rose also commented that most of the case reports proffered by Dr. Gershwin "have not studied deeply the alternative mechanisms." Tr. 280.

Various authorities have commented on the value of case reports. To start, the Federal Judicial Center has published a series of guides designed "to assist judges . . . in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer and Gladys Kessler, Reference Manual on Scientific Evidence, Preface (3d ed. 2011) ("Reference Manual"). The guidance from the Federal Judicial Center translates to the Vaccine Program because causation for off-Table injuries in the Vaccine Program is the same as traditional causation. See Moberly, 592 F.3d at 1322-23; Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1351 (Fed. Cir. 1999) ("The absence of elaboration of the law of causation in the legislative history leads us to conclude that the Vaccine Act's requirement of causation in non-Table cases was not viewed as distinct from causation in the tort law."). For examples in which appellate authorities within the Vaccine Program have cited the Reference Manual, see Germaine v. Sec'y of Health & Hum. Servs., 155 Fed. Cl. 226, 228-29 (2021), and Hart v. Sec'y of Health & Hum. Servs., 60 Fed. Cl. 598, 607 n.20 (2004).

A pertinent guide in the Reference Manual states "[a]necdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group." David H. Kaye and David A. Freedman, Reference Manual on Scientific Evidence, Reference Guide on Statistics, at 218. These authors also state "some courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under Daubert." Id. at 217 n. 14 (citing cases).

Within the Vaccine Program, the Federal Circuit has endorsed, albeit indirectly, a view that case reports merit little weight. In a series of five cases involving auto-immune hepatitis, the (undersigned) special master rejected case reports as evidence of causation. Porter v. Sec'y of Health & Hum. Servs., No. 99–639V, 2008 WL 4483740, at *13 (Fed. Cl. Spec. Mstr. Oct. 2, 2008). Under the caption of a different case, a judge at the Court of Federal Claims disagreed with this weighing of evidence. Rotoli v. Sec'y of Health & Hum. Servs., 89 Fed. Cl. 71, 86–87 (2009). When the Federal Circuit reviewed the special master's decision, the Federal Circuit stated that "[t]he special master found that the remaining two articles, both describing single case studies, did not contain any meaningful analysis about causation." Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1253 (Fed. Cir. 2012). The Federal Circuit also stated that the "decision reveals a thorough and careful evaluation of all the evidence including . . . medical literature." Id. at 1254.

Similar indirect support from the Federal Circuit is found in W.C. v. Sec'y of Health & Hum. Servs., No. 07-456V, 2011 WL 4537877, at *13 (Fed. Cl. Spec. Mstr. Feb. 22, 2011), mot. for rev. denied on this point, 100 Fed. Cl. 440, 456 (2011), aff'd, 704 F.3d 1352 (Fed. Cir. 2013). At the trial level, the (undersigned) special master declined to rely upon case reports because, among other reasons, "case reports cannot distinguish a temporal association from a causal relationship." Id. at *13. At the Federal Circuit, the appellate court focused primarily upon epidemiologic studies, which undermined the claim that the vaccine significantly aggravated the petitioner's illness. W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1360-61 (Fed. Cir. 2013). However, at the end of its opinion, the Federal Circuit stated that it "cannot say that the special master's . . . weighing of the scientific evidence was arbitrary or capricious." Id. at 1361.

Much of the foregoing analysis regarding case reports was set forth in K.O. v. Sec'y of Health & Human Servs., No. 13-472V, 2016 WL 7634491, at *11-12 (Fed. Cl. Spec. Mstr. July 7, 2016). After K.O., the Federal Circuit has not discussed case reports in a precedential opinion, leaving Porter and W.C. as the leading, although muted, words on the subject. Consequently, judges from the Court of Federal Claims have tended to defer to the special master's assessment of case reports. See, e.g., Kelly v. Sec'y of Health & Hum. Servs., 160 Fed. Cl. 316, 319 (2022) (indicating that the special master was not arbitrary in finding that case reports have limited or nonexistent value); Rus v. Sec'y of Health & Hum. Servs., 129 Fed. Cl. 672, 682 (2016) (noting the special master could reasonably afford little weight to the medical literature, including case reports). An exception to this trend is Patton v. Sec'y of Health & Hum. Servs., 157 Fed. Cl. 159 (2021). In Patton, the Court ruled that the special master "erred in his prong one analysis by discounting the evidentiary value of the case reports [petitioner's expert] submitted." Id. at 168. But, Patton does not discuss Porter or W.C. Instead, Patton relies upon Paluck v. Sec'y of Health & Hum. Servs., 104 Fed. Cl. 457, 475 (2012).[5]

[5] Paluck states "case reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value. Nonetheless, the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" Paluck, 104 Fed. Cl. at 475, quoting Campbell v. Sec'y of Health & Hum. Servs., 97 Fed. Cl. 650, 668 (2011). The case Paluck quotes, Campbell, cites to Rotoli v. Sec'y of Health & Hum. Servs., 89 Fed. Cl. 71, 86-87 (2009). However, the value of the opinion by the Court of Federal Claims seems questionable as the Federal Circuit, as noted above, reversed the outcome in Rotoli, and reinstated the special master's decision, which gave little weight to the case

Outside of the Vaccine Program, district courts have examined the value of case reports in the context of claims that drugs or a medical device harmed a person. Examples include: In re: Abilify (Aripriprazole) Products Liability Litigation, 299 F.Supp.3d 1291, 1309 (N.D. Fla. 2018) ("The difficulty with case reports is distinguishing between association and causation"); In re Tylenol (Acetaminophen) Marketing, Sales Practice, and Products Liability Litigation, 198 F.Supp.3d 446, 461 (E.D. Pa. 2016) ("It is true that case reports and anecdotal evidence alone may not be sufficient support for a causation opinion. . . . However, case reports considered in conjunction with other evidence may be an appropriate basis for an expert's causation opinion."); In re Mirena IUD Products Liability Litigation, 169 F.Supp.3d 396, 451 (S.D.N.Y. 2016) ("Case reports are generally disfavored by courts as evidence of causation because they merely describe 'reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; [they] do not isolate and exclude potentially alternative causes; and [they] do not investigate or explain the mechanism of causation.'") (citation omitted).

Although the case reports submitted by Dr. Gershwin might arguably support a theory that the flu vaccine plus statins may cause rhabdomyolysis, they do not make any suggestion that a flu vaccine plus some other factor (such as exercise) could cause rhabdomyolysis. These case reports thus do not carry petitioner's burden.

The case reports involving subjects who were not taking statins are factually distinct from Mr. Thornton's case in that two of these case reports (Kulkarni and Hursitoglu) involved different vaccines. Another case report which did not involve statins (Cheng) discussed a case of rhabdomyolysis after a flu vaccine. The subject was a 65-year-old man, and there was no mention of exercise. The authors cited to ASIA and proposed that an adjuvant may have caused the rhabdomyolysis. ASIA, which stands for autoimmune (anti-inflammatory) syndromes induced by adjuvants, has not been found to be a credible theory under the first Althen prong. See D'Angiolini v. Sec'y of Health & Hum. Servs., 122 Fed. Cl. 86, 101 (2015), aff'd, 645 F. App'x 1002 (Fed. Cir. 2016) (upholding special master's determination that the ASIA condition did not provide a reliable theory for recovery); see also Trollinger v. Sec'y of Health & Hum. Servs., No. 16-473V, 2023 WL 2521912, at *10 n.20 (Fed. Cl. Spec. Mstr. Feb. 17, 2023) (listing cases

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reports. Porter, 663 F.3d at 1253. Paluck, which cited Rotoli, was issued before the Federal Circuit reversed Rotoli.

in which special masters rejected the ASIA theory), mot. for rev. denied, 167 Fed. Cl. 127 (2023).

The other case report involving the flu vaccine without statins, Musso, discussed a 73-year-old man. There was no mention of exercise, nor a causal mechanism proposed. The authors concluded that "acute renal failure due to rhabdomyolysis should be considered one of the potential influenza side effects especially in the elderly." Musso at 2.

In sum, the underlying facts in the proffered case reports are too different from Mr. Thornton's case to provide support for the theory that the flu vaccine can cause rhabdomyolysis. See, e.g., Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357, 1365 (Fed. Cir. 2000) ("In order for the study to be instructive, however, its conclusions must fit the facts of the case under consideration") (citing Grant v. Sec'y of Dep't of Health & Hum. Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992)). The case reports regarding incidences of rhabdomyolysis in patients who were taking statins when they were vaccinated do not demonstrate that the flu vaccine in combination with non-statin factors could trigger rhabdomyolysis. The case reports involving vaccines without statins are factually distinct, either in the type of vaccine or in the traits of the subject. Moreover, these reports do not offer a reliable theory to explain how the flu vaccine may cause rhabdomyolysis, either by itself or in combination with a non-statin factor.

Special masters have frequently rejected general vaccine-induced inflammation as a theory. See, e.g., Goff v. Sec'y of Health & Hum. Servs., No. 17-259, 2025 WL 2081262, at *18 (Fed. Cl. July 9, 2025) (special master did not err in requiring evidence that inflammatory effects of influenza vaccine could induce the alleged injury); Germaine v. Sec'y of Health & Hum. Servs., 155 Fed. Cl. 226, 227 (2021) (special master did not err in rejecting inflammation theory that was not specific to the vaccine at issue); Jason v. Sec'y of Health & Hum. Servs., No. 21-835V, 2025 WL 786306, at *10 (Fed. Cl. Spec. Mstr. Feb. 11, 2025) (presence of inflammatory process by itself does not credibly point to vaccine causation without additional evidence linking the vaccine's immune response to the pathology of petitioner's actual condition).

Thus, Mr. Thornton has not met his burden under the first Althen prong. There is insufficient evidence that the flu vaccine produces the cytokines that would contribute to rhabdomyolysis. And, while it is possible that the flu vaccine, in combination with exercise, can cause rhabdomyolysis, Mr. Thornton has not presented a sound and reliable theory to explain how this would occur. The

Federal Circuit has "consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1360 (Fed. Cir. 2019).

Additionally, there remains an issue with the timing aspect of Mr. Thornton's theory. This topic is discussed next.

VII. Althen Prong Three

One portion of a petitioner's burden is to show with preponderant evidence, "a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278. The timing prong actually contains two parts. A petitioner must show the "timeframe for which it is medically acceptable to infer causation" and the onset of the disease occurred in this period. Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd without op., 503 F. App'x 952 (Fed. Cir. 2013). The expected interval depends, at least in part, upon the theory being offered. Langland v. Sec'y of Health & Hum. Servs., 109 Fed. Cl. 421, 443 (2013).

Mr. Thornton received the flu vaccine on September 30, 2016. His rhabdomyolysis manifested eleven days later, on October 11, 2016. In between, he received an anthrax vaccination on October 3, 2016. Mr. Thornton contends that this 11-day interval between flu vaccination and onset is appropriate to infer causation. He argues that some individuals may experience higher levels and longer durations of cytokine changes than average; that cytokine changes may be sustained for weeks; and that even as cytokine levels return to baseline, the biological effects continue. Pet'r's Posthear'g Br. at 15, 20, 22.

More specifically, Mr. Thornton's theory is not that the cytokines from his flu vaccine directly caused his rhabdomyolysis, but rather, that the downstream/spillover effects of these cytokines resulted in an asymptomatic level of inflammation, which then acted with his exercise to induce his rhabdomyolysis. Resp't's Posthear'g Br. at 9.

Mr. Thornton appears to argue that an extended cytokine elevation, and the lingering effects of cytokine elevation on top of this extended period, creates a window during which it is logical to infer that cytokine elevation from vaccination

caused rhabdomyolysis. First, there is the issue of the levels and duration of cytokine elevation.

There is sufficient evidence to say that cytokine expression can be variable among individuals. But, while Talaat demonstrates that certain individuals experience extreme differences in cytokine levels and in the timing of the rise/decline, the article does not necessarily indicate that the *overall duration* of change is sustained longer than average. The participants' cytokine levels "generally peak[ed] at approximately 24 hours" and decreased again within 44 hours. Talaat at 207; see also Resp't's Posthear'g Br. at 11.

While Talaat shows that IL-8 in particular may be reduced for as long as two weeks, it is unclear whether other cytokines may be impacted for this length of time. Furthermore, nowhere does Mr. Thornton explain what impact, if any, low IL-8 has on the development of rhabdomyolysis, especially as IL-8 is a proinflammatory cytokine, which would more likely be elevated with rhabdomyolysis. See Dorland's Illustrated Medical Dictionary 937 (33rd ed. 2019). Thus, although there is evidence that some individuals may experience a greater cytokine reaction, Talaat indicates that cytokines nonetheless peak within the first 24 hours.

To the extent that the Cohen article demonstrates that cytokines may be at peak elevation nearly two weeks post-vaccination, Cohen is of limited value to the case at hand because the vaccine being tested (smallpox) is not the vaccine Mr. Thornton received (flu). Lampe v. Sec'y of Health & Hum. Servs., 219 F.3d 1357, 1365 (Fed. Cir. 2000) (citing Grant v. Sec'y of Dep't of Health & Hum. Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992).

Whether the *effects* of cytokines may continue long enough to infer causation 11 days post-vaccination is a different issue. Dr. Gershwin described the cytokines as "signaling molecules." Tr. 138. He opined that once the cytokines begin the process by signaling the cells, the process continues on its own, and the cytokines are no longer needed. Id. "The effects don't stop just because the level [of cytokines] you measure that day [has] decreased. If that was true, you wouldn't see the peak of antibody responses . . . two to six weeks later after a vaccination. It's a continued effect." Id. at 288. "It's not that it stops and comes back 12 [sic] days later. It's a continuous process." Id. at 316. Put differently, even though the symptoms may subside, part of Mr. Thornton's theory is that an underlying, asymptomatic level of inflammation may continue to occur for days after vaccination. Tr. 140-41.

Dr. Gershwin commented on the variety of ways that cytokines affect the body, calling them "amongst, if not the, most promiscuous molecules in the body." Tr. 316-17. Furthermore, inflammation "is a continuous process involved in our bodies." As an example, he noted that a low dosage of aspirin has a persistent effect on a variety of cell functions despite being an "incredibly small" dose. Id. at 317.

The Secretary disputes that the effects of released cytokines can be present for weeks after the cytokines return to baseline levels. Resp't's Posthear'g Br. at 9. The Secretary argues that the side effects noted in Hervé "are the typical reactions one might expect to experience in the days immediately following a vaccination," such as fever, fatigue, headache, myalgia, and chills, and that nothing in Hervé indicates that the effects are long-lasting. Id. at 9-10.

The Secretary further notes that Cohen (which demonstrates that cytokines may peak up to 12 days after receiving the smallpox vaccine) shows that the "timeline of symptoms and side-effects that resulted from cytokine response mirrored the rise, peak, and fall of serum cytokine levels in the subjects' blood." Thus, the Secretary argues, the article also does not support the theory that the *effects* of the cytokine elevation persist after the cytokines themselves have returned to baseline. Resp't's Posthear'g Br. at 10.

Dr. Donofrio stated that he "[could not] really speak to a delayed response to the cytokine elevation, as Dr. Gershwin talked about, but the elevations occur within the first day and abate by the end of the second day." Tr. 169. When asked whether, due to the vaccine, Mr. Thornton's cytokines would have been elevated 11 or 12 days after vaccination, Dr. Donofrio stated, "No, I wouldn't think so." Id. When asked a follow-up question about whether there were any signs of symptoms present that are "directly or can be directly attributable to someone undergoing a cytokine response," Dr. Donofrio said he saw no indication of this. Tr. 169-70.

In all, Mr. Thornton has proffered evidence to show that (1) the peaks and cycles of cytokine elevation can vary significantly between individuals; (2) some vaccines can cause certain cytokines to peak nearly two weeks post-vaccination; and (3) cytokines affect the body such that the effects of cytokines may spill over and continue for some period of time even after cytokines return to baseline. However, Mr. Thornton has not shown that the flu vaccine can cause the specific cytokines which may be involved in rhabdomyolysis to peak for an extended period of time generally, or that their effects would continue for up to 11 days.

Rather, the evidence pertains to the general science of cytokines and only loosely suggests that the effects may persist for some undefined period of time. Special masters have often found that theories based on broad cytokine science are not persuasive. See Thompson v. Sec'y of Health & Hum. Servs., No. 18-1217V, 2023 WL 9053982, at *14 (Fed. Cl. Dec. 5, 2023) (citing cases). That there is an expected rise in cytokines following vaccination does not establish that a vaccine can cause a cytokine-mediated injury. See, e.g., Dean ex rel. I.D. v. Sec'y of Health & Human Servs., No. 13-808V, 2017 WL 2926605, at *17-18 (Fed. Cl. Spec. Mstr. June 9, 2017). There must be evidence to establish that the particular cytokines elevated by the particular vaccine play a role in the pathogenesis of the particular injury—and, relatedly, that the timeframe of the process aligns with the onset of a petitioner's injury after vaccination.

The evidence here provides only a vague timeframe as to the key part of the theory: how long the residual effects of elevated cytokines may last. Hervé, for example, states only that effects occur "soon after vaccination" or "early after vaccination." Hervé at 2. Although the evidence shows that it is possible that cytokine effects may last for some period of time after the cytokine levels return to baseline, there is not preponderant evidence that overall cytokine effects would last for 11 days, let alone evidence that the specific cytokines involved in rhabdomyolysis could trigger effects lasting that long. In contrast, petitioners have prevailed on prong three in cases where the onset of an injury was within a few days of vaccination. See, e.g., Fuller on behalf of B.F. v. Sec'y of Health & Hum. Servs., No. 15-1470V, 2019 WL 7576382, at *19 (Fed. Cl. Spec. Mstr. Dec. 17, 2019) (three days for febrile seizures); Bantugan v. Sec'y of Health & Hum. Servs., No. 15-721V, 2019 WL 7602581, at *21 (Fed. Cl. Spec. Mstr. Dec. 20, 2019) (three days for myocarditis). Compare Gram v. Health & Hum. Servs., No. 15-515V, 2022 WL 17687972, at *51 (Fed. Cl. Spec. Mstr. Nov. 16, 2022) (at least ten but likely more than fifteen days was too long to attribute febrile seizures to vaccination).

Thus, while the evidence shows that it is possible for cytokines to affect the body beyond the duration of their elevation, this falls short of establishing a timeframe during which one may infer that the onset of rhabdomyolysis was triggered by a flu vaccine. As Mr. Thornton has not met his burden under the first or third Althen prongs, he is not entitled to compensation. Nonetheless, the second Althen prong is addressed next.

VIII. Althen Prong Two

Pursuant to Althen, a petitioner must establish "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. A petitioner does not need to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" to satisfy this prong, but may rely on circumstantial evidence and reliable medical opinions. Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325-26 (Fed. Cir. 2006). The Federal Circuit has instructed special masters to carefully consider the views of treating doctors. Id. at 1326.

Three categories of evidence are considered in the foregoing analysis. First, there is an overview of the opinions of the doctors who treated Mr. Thornton. Next, the clinical evidence is considered, and finally, Mr. Thornton's exercise routine is discussed.

A. Treating Doctors

Mr. Thornton notes that two of his treating doctors believed that the vaccine caused him harm. A neurologist, Dr. Scully, wrote on November 14, 2016, "As best I can tell this is an autoimmune mediated process, perhaps triggered by several recent vaccinations." Exhibit 3 at 573. In March 2017, she wrote that his condition was "thought to have been associated with the administration of vaccinations." Id. at 102. In January 2018, Dr. Scully wrote that "The timing and the secondary consequences of [Mr. Thornton's] disorder strongly imply that his vaccine regimen played a causative role in development of this concern." Exhibit 8.

Neuromuscular specialist Dr. Ortega, who saw Mr. Thornton in January 2017, reported that the "initial evaluation was concerned with the possibility of overuse resulting in rhabdomyolysis, though the physical activity [Mr. Thornton] performed as part of that fitness test was within the spectrum of normal to him so one would not expect that he would have rhabdomyolysis as a consequence." Exhibit 7 at 1. Dr. Ortega "most strongly suspect[ed] that his rhabdomyolysis was induced by his exposure to vaccinations," and noted "a number of case reports describing patients who have rhabdomyolysis following a variety of vaccinations." Id. at 4.

The Secretary acknowledges that two of Mr. Thornton's treating physicians considered that his rhabdomyolysis was possibly related to vaccination, but argues that neither doctor put forth a theory causally connecting the flu vaccine to his

condition. Resp't's Prehear'g Br. at 37. Without a clear medical or scientific basis underlying these attributions, the Secretary argues, these statements do not advance Mr. Thornton's claim or establish a logical sequence of cause and effect. Id. at 37-38.

Analysis

"[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect shows that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1326 (internal quotation marks omitted). However, opinions from treating physicians are not conclusive; "Any such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court." 42 U.S.C. § 300aa–13(b)(1).

The doctors' opinions were based, in part, on temporal proximity to vaccination. Dr. Scully also based her opinion on the circumstances of Mr. Thornton's case, such as the lasting effects of his injury, but did not elaborate on what she meant by the "secondary consequences" that "strongly impl[ied]" vaccine causation. Dr. Ortega noted reports in the literature of vaccine-associated rhabdomyolysis as well as Mr. Thornton's physical fitness. As discussed above, the value and relevance of case reports is questionable, especially without knowledge of which case reports Dr. Ortega was referencing, and whether he did any research into the matter or personally reviewed these case reports. Also as discussed, that the exercises were familiar to Mr. Thornton does not necessarily indicate that his rhabdomyolysis was more likely caused by the vaccine. Additionally, neither doctor proposed a mechanism by which the vaccine may have caused Mr. Thornton's injury.

"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." Solak v. Sec'y of Health & Hum. Servs., No. 14-869V, 2020 WL 9173158, at *19 (Fed. Cl. Spec. Mstr. Feb. 19, 2020). While the views of Mr. Thornton's physicians have been considered, they do not by themselves satisfy the second Althen prong. See Isaac v. Sec'y of Health & Hum. Servs., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012) (giving little weight to physicians' notations where, "[in] contrast to cases in which the record reveals extensive analysis of the causation issue, it appears in this case that once the diagnosis of GBS was made there simply was very little medical attention paid by treating personnel to the cause of Petitioner's

illness"), mot. for rev. denied, 108 Fed. Cl. 743 (2013), aff'd, 540 F. App'x 999 (Fed. Cir. 2013).

B. Clinical Evidence

Mr. Thornton argues that the clinical evidence supports a conclusion of vaccine causation. After his collapse, Mr. Thornton had elevated levels of creatinine without dehydration. Pet'r's Posthear'g Br. at 17 (citing Exhibit 4 at 36-37). He did not have elevated hemoglobin, nor any other signs of dehydration. As Dr. Gershwin opined in his testimony, the elevated levels of creatinine without dehydration, as well as Mr. Thornton's rapid collapse, indicates that there was an ongoing process before Mr. Thornton exercised. Tr. 71-72. The ongoing level of activity was "very low" prior to the exercise, and "the exercise was a cofactor in producing the rhabdomyolysis." Id. at 77. Mr. Thornton also points to his elevated heart rate and muscle pain on October 11, both of which are signs of cytokine release in the bloodstream. Pet'r's Posthear'g Br. at 17-18; Tr. 197.

Dr. Rose explained that CK levels in cases of rhabdomyolysis are in the thousands, usually more than 5000. Tr. 240. The levels begin to rise within 12 to 36 hours of an exertional event, peak around 3 or 4 days after onset, and then begin to decrease at a rate of 30-40% per day before normalizing after weeks. Id. Dr. Donofrio stated that the normal range for CK levels is between 50 and 196. Exhibit F at 2. Holloman Air Force Base, where Mr. Thornton was treated, also cites this range, as well as a reference range of 49-392. Exhibit 11 at 62, 392.

No measurements were taken on October 11, 2016, the day of Mr. Thornton's collapse. His CK level on October 12, 2016, was 127,930. Exhibit 11 at 392. This was the highest level recorded for Mr. Thornton. Thereafter, his CK levels steadily declined, falling below 5000 on October 21, 2016 with a level of 2539. Id. at 391. The value remained in the low thousands before reaching 884 on November 7, 2016, and a low of 144 on November 23, 2016. Id. at 390-91.

Dr. Donofrio opined that Mr. Thornton's rhabdomyolysis began October 10 or October 11, 2016. Tr. 209. Dr. Rose agreed that the levels of CK on October 12, 2016, were near or after peak level. Tr. 243. Dr. Gershwin opined that Mr. Thornton would not have felt the effects of elevated CK and myoglobin prior to exercising because he was "in such good shape," so the activity "was basically clinically invisible." Tr. 78, 93.

Mr. Thornton continued to have some relatively high measurements the following year, as well as some normal levels. For example, he had measures of

512 on September 11, 2017; 182 and 233 on September 14, 2017; 569 on September 27, 2017; and 224 on October 16, 2017. Exhibit 11 at 62, 61, 50, 45, and 43. Mr. Thornton highlights these elevated levels. Dr. Gershwin stated that exercise-induced rhabdomyolysis is self-limiting; had the rhabdomyolysis been the result of exercise, one would expect it to have returned to normal "long before" the elevation in August 2017. Exhibit 117 at 3. However, he also testified that "even with the influenza vaccine plus exertional rhabdomyolysis, [he] would have expected it to be self-limiting." Tr. 144.

The Secretary notes Dr. Donofrio's opinion that Mr. Thornton's CK levels "may be considered normal" based on race and sex. Resp't's Prehear'g Br. at 36. Thus, the Secretary argues, these elevated values "could be normal and not reflect muscle pathology." Id. (quoting Exhibit F at 2). The Secretary also argues that Mr. Thornton's continuing muscle pain was not necessarily a continuation of a pathologic process, as there are many causes of muscle pain. Id. at 37.

In support of his statement regarding normal CK levels, Dr. Donofrio cites to articles by Wong and Neal. The Wong researchers found that the serum CK levels were significantly higher in black men than in other subgroups. Wong at 584. They note that these findings correspond with prior studies as well. Id. While the overall population had an average upper limit of 358, the upper limit for black men was 520. Id. at 585.

"Highly elevated creatine kinase levels in blood may indicate muscle trauma or disease. However, it is known that baseline creatine kinase levels are higher in African Americans than in whites and that they are higher in men than in women." Neal at 73. Neal found that among subjects with hypercholesteremia, black men had higher CK levels than other groups. Id. at 74. The median CK levels of "white, Hispanic, and South Asian men were similar to each other and markedly lower than those in age-matched African American men." Id. at 75. The authors noted that the absolute values of their findings were lower than the median values reported in Wong, but the relative pattern was similar. Id. at 77.

Analysis

The medical records provide only one measure of Mr. Thornton's CK level prior to his rhabdomyolysis: he had a CK level of 293 on July 24, 2014. Exhibit 11 at 184. This is still considered within the normal range for the general population. Considering the findings of Wong and Neal, Mr. Thornton's elevated CK levels a year after the onset of his rhabdomyolysis would likely be normal for his demographic as well.

Regardless, the fact remains that Mr. Thornton's high CK levels on October 12, 2016, indicate that the process may have started prior to his exercise. Following Dr. Rose's timeline, if Mr. Thornton's peak CK levels were on October 10 or October 11, 2016, then they would have started to rise 3 to 4 days prior, between October 6 and October 8. Moreover, according to Dr. Rose, this rise would have started 12 to 36 hours after a triggering event. This would place the onset of Mr. Thornton's muscle injury between October 5 and October 7, 2016. This is reinforced by Dr. Gershwin's observations regarding the elevated levels of creatinine without dehydration and Mr. Thornton's rapid collapse upon starting his exercise routine. Tr. 71-72. Further, as Dr. Gershwin opined, Mr. Thornton may not have felt the effects of his rising CK levels prior to exercising since he was in such good shape. Thus, whether or not Mr. Thornton's high CK levels were actually normal to him one year after the onset, it appears that his CK levels began to rise prior to October 11. This does not, however, establish that the flu vaccine was responsible for the rise in CK levels.

C. Exercise

Mr. Thornton argues that the sequence of events demonstrates that the vaccine caused his injury. Mr. Thornton was extremely active, and the exercises he performed when he collapsed were "neither qualitatively nor quantitatively different from pervious exercise routines he had performed regularly for years." Pet'r's Prehear'g Br. at 29. The only difference, he contends, was that he had been vaccinated in recent weeks. Mr. Thornton had not exercised since receiving the vaccine, and his theory is that the cytokines and/or their downstream effects were still present eleven days after vaccination. His vigorous exercise on October 11 then enhanced the cytokine release, resulting in his rhabdomyolysis. Id.

Additionally, Mr. Thornton contends that the Secretary's experts based their opinions on erroneous assumptions—that Mr. Thornton participated in a ruck march, and that he has a metabolic myopathy. Pet'r's Prehear'g Br. at 18. Neither expert, he states, opined that the exercise Mr. Thornton did on October 11 would be expected to cause rhabdomyolysis absent these factors. Id. at 19. He again notes that the exercise he did that day was not "non-familiar, eccentric, unaccustomed, or dramatically increased exercise" for Mr. Thornton. Id. This stands in contrast to the evidence of exercised-induced rhabdomyolysis that the Secretary provided, which focuses on unfamiliar, different, and/or increased exercise. Id.; see also Pet'r's Prehear'g Reply at 8.

The Secretary argues that, even if Mr. Thornton did not participate in a ruck march, he would not be precluded from developing rhabdomyolysis from his exercise. Resp't's Prehear'g Br. at 34. He notes that Dr. Gershwin agreed that petitioner's typical exercise routine was intense and rigorous, even without a ruck march. Id. at 35 (citing Exhibit 117 at 3 and Exhibit 130 at 2). Dr. Rose also opined that the rhabdomyolysis was a result of muscle breakdown during the PT testing. Id. (citing Exhibit A at 22).

Like Mr. Thornton, the Secretary recognizes that the exercise Mr. Thornton did during his PT test was "not qualitatively or quantitatively different" from his regular routine; however, the Secretary also highlights that, just as Mr. Thornton had exercised for years without issue, Mr. Thornton had received vaccinations for years without issue. Resp't's Prehear'g Br. at 35. He asserts that Mr. Thornton "has not identified any aspect of his clinical course that signifies his [rhabdomyolysis] was caused by the flu vaccine rather than exercise alone," and that there are many instances of rhabdomyolysis caused purely by exercise. Id. at 36. The Secretary also notes that rhabdomyolysis is often associated with eccentric exercises such as pushups; sporadic strenuous exercise; low intensity exercise; and military training. Id. at 34-35 (citing Nye; Khan; Rawson; and Knafl).

Analysis

Although the Secretary questions why Mr. Thornton was able to receive vaccinations and participate in his regular exercise regime for years with no complications, Mr. Thornton did not exercise between receiving his flu vaccine on September 30, 2016, and doing the PT test on October 11, 2016. It is unknown whether Mr. Thornton waited a longer duration before resuming exercise in previous years, or, on the other hand, if he did not take a break at all. Without knowledge of the circumstances regarding previous vaccines / exercise schedules, the comparison does not disprove Mr. Thornton's argument.

Even so, that the exercise was familiar to Mr. Thornton does not rule out exercise-induced rhabdomyolysis, either. The Clinical Practice Guidelines by Nye et al. and cited by Dr. Donofrio explain that onset usually occurs "after strenuous or non-familiar exercise training." Nye at 5 (emphasis added). As further explained, eccentric exercises are often associated with rhabdomyolysis. Id. Before his collapse on October 11, Mr. Thornton performed sit-ups (which may be eccentric depending on form) and pushups (which are eccentric). There are also reports of cases of rhabdomyolysis following low-intensity exercises. Khan at 274. Moreover, the literature discusses that it is common to see cases of rhabdomyolysis in military training. Khan at 274; Rawson at S35; Khafl at 215. In sum, although

Mr. Thornton was accustomed to these types of exercises, the familiarity of the exercise does not rule it out as the cause of Mr. Thornton's rhabdomyolysis.

D. Summary

In all, the evidence under the second Althen prong is mixed. Although two of Mr. Thornton's doctors opined that the vaccine harmed him, they did not provide a basis for these opinions beyond timing and the existence of case reports. The fact that Mr. Thornton was accustomed to exercise is relevant but not dispositive to the question of whether the exercise could have induced rhabdomyolysis. And, even if it is plausible that the downstream effects of the flu vaccine caused a muscle injury five to seven days post-vaccination, which then culminated in Mr. Thornton's rhabdomyolysis eleven days post-vaccination, Mr. Thornton has still not met his burden under the first and third Althen prongs and therefore is not entitled to compensation. See, e.g., Koehn v. Sec'y of Health & Human Servs., 2013 WL 3214877, at *29 (Fed. Cl. Spec. Mstr. May 30, 2013) (citing Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding the special master did not err in resolving the case pursuant to prong two when respondent conceded that petitioner met prong three)), aff'd, 773 F.3d 1239 (Fed. Cir. 2014).

IX. Conclusion

Mr. Thornton deserves respect for navigating his difficult disease course. However, the requirements of the Vaccine Program must be met before compensation can be awarded. Mr. Thornton has not established with preponderant evidence that a flu vaccine can cause rhabdomyolysis, or that the flu vaccine harmed him. Accordingly, he is not entitled to compensation.

The Clerk's Office is instructed to enter judgment in accordance with this decision unless a motion for review is filed. Information about filing a motion for review, including the deadline, can be found in the Vaccine Rules, available through the Court's website.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master

Appendix: List of Medical Articles Cited[1]

1. Bohan & J.B. Peters, Polymyositis and Dermatomyositis (Part I), 292 N. ENG. J. MED. 344 (1975). Filed as Exhibit A, Tab 2.

2. A. Bohan & J.B. Peters, Polymyositis and Dermatomyositis (Part II), 292 N. ENG. J. MED. 403 (1975). Filed as Exhibit A, Tab 3.

3. Rodrigo Barbosa Callado et al., Rhabdomyolysis secondary to influenza A H1N1 vaccine resulting in acute kidney injury, 11 TRAV. MED. INFECT. DIS. 130 (2013). Filed as Exhibits 122 and 141.

4. Shu-Hua Chen et al., Severe rhabdomyolysis induced renal failure in a patient after an influenza vaccination, 8 INT. J. CASE REP. IMAGES 205 (2017). Filed as Exhibit 145.

5. Matthew P. Cheng et al., Post-vaccination myositis and myocarditis in a previously healthy male, 12 ALLERGY ASTHMA CLIN. IMMUNOL. 6 (2016). Filed as Exhibit 143.

6. Jeffrey I. Cohen et al., Kinetics of serum cytokines after primary or repeat vaccination with the smallpox vaccine, 201 J. INFECT. DIS. 1183 (2010). Filed as Exhibit 160.

7. Kate M. Edwards & Robert Booy, Effects of exercise on vaccine induced immune responses, 9 HUM. VACCIN. IMMUNOTHER. 907 (2013). Filed as Exhibit 136.

8. G. Efstratiadis et al., Rhabdomyolysis updated, 11 HIPPOKRATIA 129 (2007). Filed as Exhibit 137.

9. Hatice Hamart et al., Rhabdomyolysis probably induced by influenza vaccine and fibrate, 2 EUR. J. RHEUMATOL. 169 (2015). Filed as Exhibits 123 and 139.

10. Yamina Hamel et al., Acute rhabdomyolysis and inflammation, 38 J. INHERIT. METAB. DIS. 621 (2015). Filed as Exhibit 153.

[1] All articles have been considered.

11. Caroline Hervé et al., The how's and what's of vaccine reactogenicity, 4 NPJ VACCINES 39 (2019). Filed as Exhibits 135 and 157.

12. Mehmet Hursitoglu et al., Rhabdomyolysis secondary to Tetanus Toxoid administration in a Patient Following Minor Laceration, 51 J. Clin. Pharmacol. 110 (2011). Filed as Exhibit 150.

13. Andre C. Kalil & Paul G. Thomas, Influenza virus-related critical illness: pathophysiology and epidemiology, 23 CRIT. CARE. 1 (2019). Filed as Exhibit 152.

14. J.P. Keverline, Recurrent rhabdomyolysis associated with influenzalike illness in a weight-lifter, 38 J. SPORTS MED. PHYS. FITNESS 177 (1998). Filed as Exhibit 121.

15. Emily G. Knafl et al., Rhabdomyolysis: Patterns, Circumstances, and Outcomes of Patients Presenting to the Emergency Department, 18 Ochsner J. 215 (2018). Filed as Exhibits C, Tab 4 and E, Tab 6.

16. F.Y. Khan, Rhabdomyolysis: A review of the literature, 67 NETH. J. MED 272 (2009). Filed as Exhibits C, Tab 3 and E, Tab 4.

17. Jooyoung Kim et al., Exercise-induced rhabdomyolysis mechanisms and prevention: A literature review, 5 J. SPORT HEALTH SCI. 324 (2016). Filed as Exhibit 119.

18. Hemant Kulkarni et al., Casualty of Rhabdomyolysis and Combined Tetanus, Diphtheria and Acellular Pertussis (Tdap) Vaccine Administration, 53 J. CLIN. PHARMACOL. 1099 (2013). Filed as Exhibit 149.

19. C. Musso et al., Renal Failure Secondary to Rhabdomyolysis induced by Influenza Vaccine in an Old Patient, 3 REVISTA ELECTRONICA DE BIOMEDICINA 53 (2005). Filed as Exhibit 140.

20. Ryan C. Neal et al., Relationship of Ethnic Origin, Gender, and Age to Blood Creatine Kinase Levels, 122 AM. J. MED. 73 (2009). Filed as Exhibit F, Tab 2.

21. Nathaniel S. Nye et al., Clinical Practice Guidelines for Exertional Rhabdomyolysis: A Military Medicine Perspective, 20 CURR. SPORTS MED. REP. 169 (2021). Filed as Exhibit C, Tab 8.

22. E. Plotkin et al., Influenza vaccine-a possible trigger of rhabdomyolysis induced acute renal failure due to combined use of cerivastatin and bezafibrate, 15 NEPHROL. DIAL. TRANSPLANT. 740 (2000). Filed as Exhibit 124.

23. K.S. Raman et al., Influenza vaccine-induced rhabdomyolysis leading to acute renal transplant dysfunction, 21 NEPHROL. DIAL. TRANSPLANT. 530 (2006). Filed as Exhibits 125 and 144.

24. E.S. Rawson et al., Perspectives on Exertional Rhabdomyolysis, 47 SPORTS MED. S33 (2017). Filed as Exhibits C, Tab 5 and E, Tab 5.

25. E. Sevketoglu et al., Exertional rhabdomyolysis after influenza A (H3N2) infection in a basketball player boy, 31 ANN. TROP. PAEDIATRI. 93 (2011). Filed as Exhibit 120.

26. S.V. Shah & K. Reddy, Rhabdomyolysis with acute renal failure triggered by the seasonal flue vaccination in a patient taking simvastatin, BMJ CASE REPORTS (2010). Filed as Exhibit 148.

27. A. Siriwardana et al., Rhabdomyolysis Secondary to Seasonal Influenza Vaccine in a Renal Transplant Recipient, CONFERENCE DESIGN 2015-2016. Filed as Exhibit 146.

28. K.R. Talaat et al., Rapid changes in serum cytokines and chemokines in response to inactivated influenza vaccination, 12 INFLUENZA OTHER RESPIR. VIRUSES 202 (2018). Filed as Exhibit 161

29. E.T. Wong et al., Heterogeneity of Serum Creatinine Kinase Activity among Racial and Gender Groups of the Population, 79 AM. J. CLIN. PATHOL. 582 (1983). Filed as Exhibit F, Tab 1.

30. Goknur Yorulmaz et al., Fibrate therapy predispose to influenza vaccine-induced rabdomyolysis, POSTER SESSION ONLINE (2015). Filed as Exhibit 147.