In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

* *		
HAYLEY STRICKER,	*	
	*	No. 18-56V
	*	Special Master Christian J. Moran
Petitioner,	*	
v.	*	
	*	Filed: January 2, 2024
SECRETARY OF HEALTH	*	
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	
* *		

Andrew D. Downing, Downing, Allison & Jorgenson, Phoenix, AZ, for Petitioner; Nina Ren, United States Dep't of Justice, Washington, D.C., for Respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Hayley Stricker alleges a human papillomavirus vaccine caused her to suffer systemic lupus erythematous ("SLE"). She retained a rheumatologist, Thomas Zizic, to support her claim. The Secretary denied she was entitled to compensation and presented opinions from two people---a rheumatologist, Carlos Rose, and an immunologist, James Moy. Ms. Stricker, her mother, a friend, a teacher, and these doctors testified at a hearing.

[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.

Ms. Stricker has not demonstrated that she is entitled to compensation. The primary obstacle is that she has not supported Dr. Zizic's opinion that an HPV vaccine can cause SLE. Multiple reliable epidemiologic studies have searched for an increased incidence of SLE after HPV vaccination and failed to detect an increase. This epidemiologic evidence undermines Ms. Stricker's claim. Ms. Stricker has not otherwise presented theories with sufficient evidentiary value to carry her burden. Thus, she is not entitled to compensation. A full discussion follows.

I. Events in Ms. Stricker's Life

Ms. Stricker's life is organized in four periods, followed by a summary.

A. Early Life through Vaccination

Ms. Stricker's mother is Jennifer Stricker, and Jennifer's Stricker's health contributes to Ms. Stricker's claim that the HPV vaccination caused her to suffer SLE. Jennifer Stricker was born in 1963. Tr. 50. She gave birth to Hayley in 1993.

By 2015, Jennifer Stricker was diagnosed with multiple sclerosis. Tr. 53; see also Exhibit 14 at 2 (noting a family history of multiple sclerosis). Multiple sclerosis is considered an autoimmune disease, meaning doctors understand that the body's immune system attacks the central nervous system. Tr. 325; see also W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1354 (Fed. Cir. 2013) (defining multiple sclerosis). Ms. Stricker's multiple sclerosis appears particularly severe as the disease prevented her from working in her career as a dental hygienist and prevents her from driving. Tr. 27, 53.

Dr. Zizic opined that Jennifer Stricker's multiple sclerosis placed Hayley Stricker at greater risk for developing an autoimmune disease, such as SLE. Tr. 203. Dr. Rose elaborated on this point with more sophistication. According to Dr. Rose, if multiple sclerosis is associated with certain genes, if Jennifer Stricker has those specific genes, if SLE is associated with certain genes, if the genes associated with multiple sclerosis match the genes associated with SLE, and if Jennifer Stricker passed on those genes to her daughter, then Hayley Stricker could have an increased genetic susceptibility to developing SLE. Tr. 589-90, 627.

In any event, Hayley Stricker's health was mostly typical for her first two decades. In high school, Ms. Striker ran cross-country and participated in other

sports. Tr. 21, 65, 77. She began practicing yoga and worked at the front desk of a yoga studio. Tr. 21-22, 77.

When in high school, Ms. Stricker developed acne, for which she saw a dermatologist, Thomas Breza. Tr. 113. In 2010, Dr. Breza prescribed a medication for acne, minocycline, that she took for several years. Tr. 97. Ms. Stricker's use of minocycline is a foundation for Dr. Rose's theory that Ms. Stricker developed drug-induced lupus. Tr. 529, 607, 612.[2]

After high school, Ms. Stricker attended Florida Atlantic University for basic credits. Tr. 78. She continued to practice yoga and became certified as a yoga instructor in 2014. Exhibit 1 (affidavit) ¶ 3, Tr. 22, 66, 78-79.

From Florida Atlantic University, Ms. Stricker applied for a dental hygienist program at Broward County College. Tr. 78-80. Ms. Stricker was interested in becoming a dental hygienist because she had watched her mother work when she was younger and liked the work and environment. Tr. 135. She was one of 16 applicants accepted into the program. Tr. 332.

The dental hygienist program required an annual physical exam. Tr. 84. Thus, Ms. Stricker saw her primary care physician, Janet Robinson, on July 27, 2015. Exhibit 14 at 8; Tr. 84. Dr. Robinson recorded that Ms. Stricker has a "very healthy diet and exercises." Exhibit 14 at 8; accord Tr. 83, 86. The record documents that Ms. Stricker has no fatigue. Exhibit 14 at 9; Tr. 86. Ms. Stricker's skin was assessed as normal. Dr. Robinson did not see any joint swelling. Exhibit 14 at 9; Tr. 87.

Dr. Robinson ordered routine blood work. Tr. 87. The results were normal. Exhibit 14 at 61. The testifying experts generally agreed that the blood tests were normal. Tr. 216-18, 243-44, 624.

Based on the normal blood test results in July 2015, Dr. Zizic reasoned that (a) the agent inciting her SLE must have been encountered after July 2015, or (b) Ms. Stricker had antibodies that were not detected in this testing. Tr. 350. Dr. Rose responded to this last point by noting that Dr. Robinson did not order a test for a common marker for autoimmune diseases, an anti-nuclear antibody test. Tr.

[2] Minocycline is a type of tetracycline. Another type of tetracycline is doxycycline. See Dorland's at 1876 (defining tetracycline). Because Ms. Stricker eventually was prescribed doxycycline, the parties and their experts sometimes refer to Ms. Stricker's use of tetracyclines.

628. Thus, the lack of testing means she could have had antibodies, making minocycline a potential cause. Tr. 629.

On August 11, 2015, Ms. Stricker saw her dermatologist, Dr. Breza, because of acne on her face. At this appointment, Dr. Breza changed her medication from minocycline to doxycycline hyclate 100 mg. Exhibit 11 at 6, Exhibit 74 (affidavit) ¶ 1, Tr. 97. Ms. Stricker sought a second opinion from a different dermatologist, Dr. Green. Exhibit 8 at 5 (Aug. 21, 2015); Exhibit 74 (affidavit) ¶ 1. Dr. Green changed the doxycline hyclate to Acticlate 150mg. Id.; see also Pet'r's Br., filed May 13, 2022, at 4-5, Resp't's Br., filed July 12, 2022, at 12.

Around the same dates she was seeing the dermatologist, Ms. Stricker also saw her gynecologist, Dr. Bernstein, in a return appointment. Exhibit 7 at 83 (August 11, 2015). During this appointment, Ms. Stricker had her first Pap smear. Tr. 88. The Pap smear is a test to detect, among other problems, infections with human papillomavirus and cervical cancer. Dorland's at 1866. Ms. Stricker's Pap smear detected that she was infected with a strain of the human papillomavirus. Exhibit 7 at 116. The detection of this infection provides little information about when she first developed the infection. Tr. 604, 680; see also Tr. 242-43. Ms. Stricker most recently could have contracted a sexually transmitted disease, such as an HPV infection, in 2014. Exhibit 7 at 83 ("Last partner – 2014"), Tr. 88-89, 124.

Infections with human papillomaviruses can cause SLE. Tr. 169 (Dr. Zizic), 602 (Dr. Rose). Whether the latency between the infection of SLE and the first manifestation of SLE is appropriate is a point of disagreement among the experts. Tr. 604, 681. A long latency might be appropriate because the virus can lie dormant and replicate years later. Tr. 604-06, 680-81.

Although, as revealed by the Pap smear, Ms. Stricker was infected with one strain of the human papillomavirus by August 11, 2015, the vaccine could protect her against other strains. Tr. 23-24, 90. Thus, Ms. Stricker scheduled a return visit. In the September 29, 2015 appointment with Dr. Bernstein, Ms. Stricker received a dose of the human papillomavirus vaccine. Exhibit 6 at 2; Tr. 24, 82. She did not receive any other vaccines that day. Tr. 91. Ms. Stricker alleges this HPV vaccination caused her to develop SLE.

B. Vaccination through One Year Later

In the first weeks after the vaccination, Ms. Stricker appeared to be fine. She was attending school to be a dental hygienist. Tr. 24; see also Tr. 166 (Dr.

Zizic indicating that Ms. Stricker began having symptoms of SLE about six weeks after the vaccination).

Ms. Stricker returned to her dermatologist, Dr. Green, on October 21, 2015. Exhibit 8 at 3. The prescription for Acticlate was continued. Id.

Approximately one month after the September 29, 2015 vaccination, Ms. Stricker began to have health problems that interfered with her usual activities. See Exhibit 1 ¶ 5, Tr. 24 (Jennifer Stricker's testimony that Hayley's knees and ankle hurt), 66 (Ms. Stricker's testimony that one month after vaccination, Ms. Stricker could not get out of bed), 91-93 (testimony that she was fatigued in early November 2015), 338 (testimony of a school instructor that Ms. Stricker informed her that her hands hurt, possibly in October 2015).

By mid-November, Ms. Stricker was having more troubles in her musculoskeletal system. She was using medical tape to stabilize her wrists as she tried to perform varies techniques in her dental hygienist program. Tr. 25-27, 94. She was having numbness in her fingers. Tr. 27, 92. She stopped her yoga workouts. Tr. 26, 95.

In the middle of November, Ms. Stricker searched the internet for possible causes of her symptoms. Based upon the information she found, Ms. Stricker stopped taking doxycycline. Exhibit 15 at 9 (Dr. Saba's Dec. 29, 2015 report indicating that Ms. Stricker stopped taking doxycycline around Thanksgiving); Tr. 31, 98-99, 101, 113. Once she stopped, she did not resume taking doxycycline. Tr. 98.

By Thanksgiving, Ms. Stricker was in so much pain that she begged her mother to schedule an appointment with Dr. Robinson. Jennifer Stricker did so, but the earliest appointment was on December 4, 2015. Tr. 28-29, 95-96.

Before Ms. Stricker's appointment with Dr. Robinson, Ms. Stricker was scheduled for a return appointment with her gynecologist to receive the second dose of the HPV vaccine. Exhibit 2 ¶ 9, Tr. 29. However, Jennifer Stricker had a "gut feeling" that the September 29, 2015 HPV vaccine caused the decline in her daughter's health. Thus, Jennifer Stricker canceled this appointment. Id. Hayley Stricker has not received a second dose of the HPV vaccine.

The appointment with Dr. Robinson took place, as scheduled, on December 4, 2015. In the history, Dr. Robinson memorialized Ms. Stricker's complaint that her joint pain and a rash started three weeks ago. Exhibit 14 at 1. The Secretary noted that if "three weeks" were exactly 21 days, then the problems would have

started on November 13, 2015 (or 46 days after the vaccination). Resp't's Br. at 12. However, ample and persuasive evidence places the onset of Ms. Stricker's symptoms of SLE around November 1, 2015. Tr. 100. The testifying experts proposed November 1, 2015 as the beginning of Ms. Stricker's lupus, regardless of whether the lupus was systemic lupus erythematosus or drug-induced lupus. Tr. 214 (Dr. Zizic), 219 (same), 470 (Dr. Rose). Dr. Rose further opined that the acute onset of Ms. Stricker's symptoms reminded him of patients he has diagnosed as suffering from drug-induced lupus. Tr. 531-32.

Dr. Robinson's report also contains a discrepancy regarding Ms. Stricker's use of doxycycline hyclate. Dr. Robinson's history states: "[Ms. Stricker] has a long [history of] acne, currently on 150 mg of doxycycline hyclate from Dr. Green with control of her acne . . . back on doxy since August." Exhibit 14 at 1. However, preponderant evidence, including Dr. Saba's December 29, 2015 report and the testimony from Ms. Stricker, establishes that Ms. Stricker stopped her anti-acne medication before seeing Dr. Robinson.

As to the problems for which Ms. Stricker scheduled the appointment with Dr. Robinson, Dr. Robinson's history memorializes that Ms. Stricker received the HPV vaccine on September 29, 2015. Exhibit 14 at 1. Ms. Stricker complained of "sudden onset of constant episodes of moderate lower back, bilateral shoulder, bilateral hand, bilateral finger(s) and right knee arthralgias, described as aching, radiating to the bilateral foot." Exhibit 14 at 1; see also Tr. 100.

Upon examination, Dr. Robinson did not perceive any joint swelling. Id. at 3. Dr. Robinson assessed Ms. Stricker as having "Arthralgia of multiple sites." Id. Dr. Robinson ordered a series of lab tests. Id.; see also Tr. 103.

Jennifer Stricker and Ms. Stricker testified that they talked to Dr. Robinson about a potential role for the HPV vaccine. Tr. 31, 44, 102. As to the possible cause of the problems, Dr. Robinson wrote: "We are going to put the doxycycline on hold in case this is a hypersensitivity reaction. Could be related to her Gardasil vaccination but it has been over two months ago." Exhibit 14 at 3.

The laboratory returned the results on December 8, 2015. Exhibit 14 at 17-20. Some results fell outside of the expected range. For example, Ms. Stricker had high levels of globulin, alkaline phosphatase, C-reactive protein, and erythrocyte sedimentation rate. Id. at 18; see also Tr. 222-23 (Dr. Zizic).

Dr. Robinson discussed these results with Jennifer Stricker and directed Ms. Stricker to bring the results to her next dermatology visit. Exhibit 14 at 17. Dr. Robinson also referred Ms. Stricker to a rheumatologist. Id.

The dermatology appointment with Dr. Green occurred the next day, December 9, 2015. Exhibit 8 at 1. There is a note to "D/C [presumably "discontinue"] Acticlate 150 mg." Id. In the circumstances of other health problems, Ms. Stricker was much less concerned about acne. Tr. 102.

For Ms. Stricker's training to become a dental hygienist, a significant test was scheduled for December 11, 2015. Exhibit 1 (affidavit of Hayley Stricker) ¶ 13. Ms. Stricker was responsible for bringing a person, who would act as a patient, and was expected to demonstrate techniques of a dental hygienist on this person. For this process, Ms. Stricker chose her mother. Tr. 34, 106-07, 342. Ms. Stricker could not move easily and experienced a great deal of pain. Tr. 35. While in the car going home, Ms. Stricker cried. Tr. 35.

As a result of Ms. Stricker's health problems, the family canceled a vacation trip to Disney. Exhibit 2 ¶ 17, Tr. 37. They also pursued an appointment with a rheumatologist more aggressively. Tr. 38.

Ms. Stricker was able to schedule an appointment with a rheumatologist, Jihan Saba, on December 29, 2015. Exhibit 15 at 9.[3] The history Dr. Saba recorded indicated that Ms. Stricker had taken minocycline for four years but switched to doxycycline in August. Id. Ms. Stricker also informed Dr. Saba that she had stopped taking doxycycline "shortly after her joint symptoms started." Id. Dr. Saba was informed that Ms. Stricker received "the first dose of Gardasil vaccine just prior to the onset of her symptoms." Id. Ms. Stricker's symptoms included "sudden onset of joint pain and swelling . . . involving the small joints of the hands, elbows, shoulders, feet and right knee." Id.; see also Tr. 39. Dr. Saba memorialized results from the laboratory studies from earlier that month. Exhibit 15 at 9. On examination, Dr. Saba detected swelling in various joints. Id. at 10.

Based upon this information, Dr. Saba assessed Ms. Stricker as suffering from "connective tissue disease." Exhibit 15 at 12. Dr. Saba stated that she informed Ms. Stricker and her mother that "the features of connective tissue

[3] Dr. Zizic is familiar with Dr. Saba and invited her to join his practice. Dr. Saba declined because she moved out of the area. Tr. 234-35. Dr. Zizic did not speak to Dr. Saba about Ms. Stricker's case. Tr. 284.

disease may frequently change over time with a diagnosis may need to be changed." Id.

Dr. Saba's note indicates that this was part of a "long conversation." Id. Jennifer Stricker testified that Ms. Stricker and she asked Dr. Saba about minocycline as a potential cause. Exhibit 2 ¶ 18, Tr. 39, 45; see also Tr. 136 (testimony of Ms. Stricker). According to Jennifer Stricker, Dr. Saba left the room, came back, and told them that minocycline could not have been the cause because the drug would have left Ms. Stricker's body. Id. Dr. Saba's record corroborates that they discussed "drug-induced lupus as a possibility." Exhibit 15 at 12. Dr. Saba wrote that minocycline can cause drug-induced lupus but that Dr. Saba "could not find much information in the literature regarding doxycycline induced lupus." Id.

Jennifer Stricker also testified that Ms. Stricker and she asked about the HPV vaccine as a potential cause. Tr. 39; see also Tr. 110 (testimony of Ms. Stricker). According to Jennifer Stricker, Dr. Saba stated that the HPV vaccine could have been a trigger. Id. However, Dr. Saba's December 29, 2015 medical record does not memorialize any discussion about the HPV vaccine. See Exhibit 15 at 9-12.

Dr. Saba ordered an additional set of laboratory studies and prescribed a low dose of prednisone. Exhibit 15 at 12; see also Tr. 109. Dr. Saba recommended that after some additional testing, Ms. Stricker take hydroxychloroquine. Exhibit 15 at 12. The laboratory results contained some abnormal values. Id. at 67; see also Tr. 226-27.

After Dr. Saba diagnosed Ms. Stricker as suffering from a connective tissue disease on December 29, 2015, the remaining medical records carry less value in determining whether the September 29, 2015 HPV vaccine caused her rheumatological problem. Thus, these additional records are presented more summarily.

In January 2016, Ms. Stricker notified the government about her potential adverse reaction by submitting a form to the Vaccine Adverse Events Reporting Service. Exhibit 77.[4] Ms. Stricker indicated that she received the vaccine on

[4] Although Hayley Stricker is listed as the person completing the form, Jennifer Stricker stated she filled out the form for her daughter. Exhibit 77 at 3. The submitter of the form is not a fact material to outcome of this case.

October 29, 2015. Id. at 1 (box 10). However, Ms. Stricker actually received the vaccine on September 29, 2015. See Tr. 111-12.

Dr. Saba determined that the lab results indicated that Ms. Stricker could start taking hydroxychloroquine. Exhibit 15 at 63 (Jan. 4, 2016); see also Tr. 109. The medications improved Ms. Stricker's condition. Tr. 105. Ms. Stricker resumed her classes to become a dental hygienist. Tr. 41, 45.

Ms. Stricker saw a second rheumatologist, Christine Savage, on February 23, 2016. Exhibit 17 at 43. The reason for the visit was Dr. Robinson's referral. Id. Jennifer Stricker testified that the appointment was made much earlier. Tr. 43. Dr. Savage's medical history is more-or-less consistent with the above recitation of events. For example, Dr. Savage indicates that Ms. Stricker "correlates that her symptoms started a few months after switching her acne medication from minocycline to doxycycline, and receiving a [Gardasil] injection." Exhibit 17 at 43. Dr. Savage recounted that Ms. Stricker was taking prednisone and Plaquenil. Together, "the combination of prednisone and Plaquenil has resolved 90% of her joint pain symptoms." Id. at 44. In her assessment, Dr. Savage included different conditions, including "CTD [connective tissue disease]." Id. at 46; accord Tr. 43.

According to Jennifer Stricker, Dr. Savage stated that neither minocycline nor doxycycline would have caused Ms. Stricker's condition. Tr. 44. Jennifer Stricker also testified that Dr. Savage said the HPV vaccine was the trigger. Id.; Exhibit 1 (Ms. Stricker's affidavit) ¶ 26. However, Jennifer Stricker acknowledged that Dr. Savage's note does not say much about minocycline, doxycycline, or the HPV vaccine. Tr. 45; see also Exhibit 17 at 46.

The February 23, 2016 appointment appears to be the only visit with Dr. Savage. Thereafter, Ms. Stricker continued to see Dr. Saba as her rheumatologist.

Dr. Saba continued to see Ms. Stricker periodically. Exhibit 15, passim. During appointments, Dr. Saba adjusted medications. Tr. 116. By the end of February 2016, Dr. Saba was recommending a taper of prednisone. Exhibit 15 at 52; see also Tr. 125 (Ms. Stricker indicating she last took prednisone in May 2016).

C. Lupus Diagnosis

In December 2018, Ms. Stricker saw Dr. Robinson as part of an annual exam. Exhibit 33 at 1. In the review of systems, Dr. Robinson recorded that Ms. Stricker had "joint stiffness or swelling and cold extremities, but no joint pain, no weakness of muscles or joints." Id. at 2. For the physical examination, Dr.

Robinson did not comment, either affirmatively or negatively, about Ms. Stricker's joints. Id. at 3. Dr. Robinson ordered more laboratory studies.

One of the lab tests revealed that Ms. Stricker had a double-stranded DNA antibody. Exhibit 31 at 1; see also Tr. 115. After learning this information and evaluating Ms. Stricker, Dr. Saba changed the diagnosis to systemic lupus erythematous. Exhibit 35 at 4; see also Tr. 45, 115, 166-68. Dr. Zizic explained that antibodies against double-stranded DNA are 99 percent specific for lupus. Tr. 240. Dr. Rose agreed that the diagnosis was most likely systemic lupus erythematosus. Tr. 529. However, Dr. Rose stated that even after the detection of anti-double stranded DNA antibodies, drug-induced lupus remains a potential diagnosis for Ms. Stricker. Tr. 529, 630.

D. Currently[5]

Although Ms. Stricker graduated from the program to become a dental hygienist and worked for a time as a dental hygienist, she found she could not perform the duties. Tr. 118. Instead, Ms. Stricker works for a yoga studio where she directs teachers of yoga. Tr. 48, 55, 121, 141.

In recent medical records from Dr. Saba, Ms. Stricker denied having a list of problems including "joint pain, joint swelling, morning stiffness, rashes, photosensitivity." Exhibit 92 at 2 (Aug. 17, 2021); accord Exhibit 87 at 9 (Feb. 16, 2021), Exhibit 87 at 1 (Aug. 13, 2020). When these records were pointed out to Ms. Stricker on cross-examination, she stated that she is frustrated with Dr. Saba. To Ms. Stricker, Dr. Saba asks questions like an "auctioneer" and does not write down information that Ms. Stricker conveys to her. Tr. 128-31; see also Tr. 149 (redirect examination). Ms. Stricker has considered changing rheumatologists; however, she ultimately decided to continue with Dr. Saba, as she knows Ms. Stricker's history. Tr. 134.

Dr. Saba has continued to prescribe hydroxychloroquine, and while on this medication, Ms. Stricker has not experienced new symptoms. Tr. 116, 147-48. Dr. Rose opined that Ms. Stricker's disease is "mild," potentially controlled with the hydroxychloroquine. Tr. 470. Dr. Rose further opined that the use of medication interferes with determining whether Ms. Stricker's lupus is "active" right now. Tr. 539, 763. If Ms. Stricker were his patient, Dr. Rose might consider carefully and slowly tapering the hydroxychloroquine. Tr. 540-41, 615, 620.

[5] The witnesses testified in January 2022.

E. Summary

A few events in Ms. Stricker's life are key to understanding the positions of the parties and the experts they have retained. Ms. Stricker's mother suffers from an autoimmune disease, which might increase Ms. Stricker's susceptibility to developing an autoimmune disease. Before the vaccination, Ms. Stricker was exposed to various substances associated with lupus. These include the medications for acne, minocycline and doxycycline. Before the vaccination, Ms. Stricker also became infected with the human papillomavirus, although the date of infection was more than one year before the vaccination.

Ms. Stricker received the first dose of the HPV vaccine on September 29, 2015. She developed symptoms of lupus around November 1, 2015. The symptoms, such as joint pain, progressed, and Ms. Stricker was diagnosed with a connective tissue disease. Approximately two years later, Ms. Stricker's diagnosis was changed to systemic lupus erythematosus.

Ms. Stricker alleges that the HPV vaccine caused her to develop SLE. The prominent events regarding her claim are discussed next.

II. Procedural History

Ms. Stricker began this litigation by filing her petition on January 11, 2018. With her petition, Ms. Stricker submitted affidavits from herself and from her mother. Exhibits 1-2. She periodically filed medical records.

Within a month of filing the petition, Ms. Stricker submitted letters from doctors who treated her. Exhibits 22-25. The rheumatologist, Dr. Saba, stated that Ms. Stricker's mother "asked me to give my opinion on whether her connective tissue disease may have been triggered by the [Gardasil] vaccine since she would like to pursue with the vaccine injury program." Exhibit 22 (dated Jan. 31, 2018). Dr. Saba's response was indeterminant:

> It is known that connective tissue disease[s] have both an underlying genetic component and an environmental trigger which can be an infection, environmental pollutants, smoking, vaccines, psychological distress etc. Because of the chronological timing of the vaccine vis-à-vis the onset of her symptoms it is very possible that it was the environmental trigger in her case.

Id.

The letter from Ms. Stricker's primary care physician, Dr. Robinson, spoke more supportively of the claim. Dr. Robinson wrote that Ms. Stricker "received her first Gardasil vaccination on 9/29/15 and her symptoms started around mid November of 2015 so it does seem likely that her autoimmune disease was trigger[ed] by the vaccine." Exhibit 23 (dated Jan. 9, 2018).

A third treating doctor, the dermatologist (Dr. Breza), also wrote a letter on Ms. Stricker's behalf. Dr. Breza explained that when patients with minocycline-induced lupus stop taking the medication, "the symptoms and blood serologies resolve." Exhibit 24 at 1. For support, Dr. Breza submitted the article by Lawson and others. Dr. Breza also commented that Ms. Stricker's symptoms "have not resolved several years after discontinuation of minocycline." Id. Thus, Dr. Breza "can be certain that minocycline was not the cause of her connective tissue disorder." Id.

After filing more medical records, Ms. Stricker supported her claim by filing a report from Dr. Zizic on February 14, 2019. Exhibit 37. Dr. Zizic stated that Ms. Stricker suffered from systemic lupus erythematosus, not "minocycline-induced systemic lupus erythematosus." Id. at 42. For a theory to explain how an HPV vaccine can cause systemic lupus erythematosus, Dr. Zizic proposed molecular mimicry. Id. at 28, 34-39. Dr. Zizic also discussed granzyme B. Id. at 30. However, this presentation was not clear and in a March 12, 2019 status conference, Ms. Stricker clarified that her theory was molecular mimicry.

The Secretary responded to Dr. Zizic's report by obtaining a report from Dr. Moy. Exhibit A (filed June 14, 2019). The Secretary added a report from Dr. Rose on September 13, 2019. Exhibit L.

Dr. Moy agreed that Ms. Stricker suffers from SLE. Exhibit A at 6. Dr. Moy stated that the HPV vaccination did not cause Ms. Stricker's SLE. In support, Dr. Moy generally relied upon epidemiologic studies. Id. at 5. Dr. Moy appeared to indicate that Ms. Stricker's HPV infection, which she developed before the vaccination, could have caused her SLE. Id. at 6. Dr. Moy did not raise any challenges to molecular mimicry. See Exhibit A.

Dr. Rose questioned whether Ms. Stricker suffered from SLE or from drug-induced lupus. Exhibit L at 9-11. Citing various epidemiologic studies, Dr. Rose questioned whether an HPV vaccine can cause systemic lupus erythematosus. Id. at 13-18. Dr. Rose proposed that Ms. Stricker might have drug-induced lupus. Alternatively, Dr. Rose proposed that Ms. Stricker's SLE occurred spontaneously. Id. at 19, 22.

Dr. Zizic addressed the opinions of Dr. Moy and Dr. Rose in a report filed on January 3, 2020. Exhibit 75. Dr. Zizic disagreed with Dr. Rose's suggestion that Ms. Stricker could have drug-induced lupus. Id. at 1. Dr. Zizic also disputed Dr. Moy's suggestion that an HPV infection caused Ms. Stricker's SLE. Id. at 10. Finally, Dr. Zizic challenged the epidemiologic studies on which the Secretary's experts had relied. Id. at 2-9.

In the January 20, 2020 status conference, the parties were asked whether they wanted to retain epidemiologists. However, the parties demurred. Thus, Dr. Zizic's report completed the stage in which experts disclosed their opinions.

The parties were directed to submit additional material in advance of a potential adjudication. Order, issued Jan. 9, 2020. Ms. Stricker filed her brief and other materials on or before March 31, 2020.[6] The Secretary submitted his materials on June 22, 2020. Ms. Stricker filed a reply on July 22, 2020.

The undersigned determined that a hearing to receive oral testimony was appropriate. Order, issued Feb. 19, 2021. The parties determined that mutually convenient dates for the hearing was January 18, 2022 to January 21, 2022.

The hearing proceeded as scheduled. Ms. Stricker, Jennifer Stricker, a friend, and a teacher from Ms. Stricker's dental hygienist program testified about Ms. Stricker's health and activities. Dr. Zizic testified on behalf of Ms. Stricker, opining that the HPV vaccination caused Ms. Stricker to suffer SLE. Dr. Rose and Dr. Moy testified on behalf of the Secretary. During the hearing, the Secretary attempted to elicit testimony from Dr. Moy regarding molecular mimicry. However, Ms. Stricker objected on the ground that Dr. Moy did not disclose any opinions regarding molecular mimicry in his reports. Tr. 652. This objection was sustained, and a portion of Dr. Moy's testimony was struck. Tr. 666.

Following the hearing, the parties submitted briefs responding to questions. See Pet'r's Posthear'g Br., filed May 13, 2022; Resp't's Posthear'g Br., filed July 12, 2022; Pet'r's Posthear'g Reply, filed Aug. 11, 2022. Ms. Stricker later

[6] During the briefing stage, Ms. Stricker was awarded attorneys' fees and costs on an interim basis. First Fees Decision, 2020 WL 1028901, issued Feb. 6, 2020. After the hearing, Ms. Stricker was given a second interim award of attorneys' fees. Second Fees Decision, 2022 WL 2387994, issued Nov. 4, 2022. Her request for costs was deferred. Id. at *4.

submitted a notice of additional authority to which the Secretary responded. These submissions make the case ready for adjudication.

III. 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).

IV. Althen Prong 1

To meet her burden regarding the first Althen prong, Ms. Stricker advances the opinions of Dr. Zizic and the articles on which he relies. Pet'r's Posthear'g Br. at 28-57. Ms. Stricker offers the theory of molecular mimicry, although she may, as discussed below, have added a second theory involving granzyme B. The Secretary, on the other hand, challenges Ms. Stricker's evidence by putting forward opinions from Dr. Moy and Dr. Rose as well as the articles on which they rely. Resp't's Posthear'g Br. at 7-20.

The parties offer various types of articles, which could be relevant to any causal theory. Thus, epidemiological studies, studies on the effects of vaccination, and case reports are discussed first in Sections IV.A through IV.C below. After those sets of foundational materials are examined, the two theories are analyzed in Section IV.D.

A. Epidemiologic Studies[7]

For a lengthy discussion of the value of epidemiologic studies in the Vaccine Program, see Tullio v. Sec'y of Health & Hum. Servs., No. 15-51V, 2019 WL 7580149, at *5-8 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448, 475 (2020). Here, the parties have introduced multiple epidemiologic studies. They are presented in chronological order, beginning with the study that was published earliest.

1. Chao

After the Food and Drug Administration licensed Gardasil, Merck undertook a safety study. Chao at 194, Tr. 416. Researchers, including some employees at Merck Research Laboratory, studied women in two managed-care organizations, Kaiser Permanente Southern California, and Kaiser Permanente Northern California. Chao at 194. Merck "had significant input into the study design and analytic plan, all pre-specified in a protocol that was approved by FDA." Chao at 202, Tr. 362-64. Merck also "took part in the review of analysis and drafting and revising the manuscript." Chao at 202, accord Tr. 560. However, "Kaiser Permanente authors held final decision power about all editorial suggestions." Chao at 202.

Using databases, the researchers identified 189,629 women who received an HPV vaccination. Practically all the women were ages 9-26 years old. Chao at 194. These women were followed for 180 days after receiving a vaccination. Id. Dr. Zizic and Dr. Rose disputed whether 180 days was sufficiently long. Tr. 373, 417, 430-32, 794.

Within the vaccinated cohort, researchers looked for potential new autoimmune diseases, including systemic lupus erythematosus. Chao at 194. "The method for case identification was designed to be highly sensitive to capture any potential cases, to address potential undercoding or miscoding in the early course

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

of an autoimmune condition." Researchers consulted ICD-9 codes, abnormal lab values, and pharmacy prescription records. Chao at 195, Tr. 419- 21.

Investigators removed any women who had been enrolled in the managed-care organization for less than 12 months. Chao at 195. Investigators also removed anyone with pre-existing autoimmune diseases. Id. Then, a case review committee ("CRC") looked at the medical records. "The rheumatology CRC consisted of one paediatric and two adult rheumatologists." Id. The CRC evaluated the diagnosis and determined the date of the onset. Id., Tr. 574. For cases involving SLE and four other conditions, researchers reviewed only a sample of potential cases. Chao at 195. The CRC members were masked to the person's date of vaccination. Id. Tr. 424, 729. The authors presented this process in Table 1. Tr. 371, 375, 566-67.

The above process (detecting autoimmune diseases among the vaccinated population) seems relatively uncontroversial. The controversial part of Chao concerns how researchers estimated the background (or incidence) of autoimmune diseases in the unvaccinated.

Unvaccinated people began accruing time in the study either when they were members of the managed-care organization for twelve months or in August 2006, which is when the study began. Chao at 195. The accrual of a person's time ended on the later of (1) the date of disenrollment, (2) the date of their first vaccination, or (3) the end of September 2008. Chao at 195. As Dr. Rose said, an unvaccinated person became a vaccinated person, meaning the unvaccinated and vaccinated groups comprised the same people. Tr. 422, 633, 636-37, 728.

To identify potential new-onset autoimmune conditions in the unvaccinated population, the investigators used "the same identifying algorithm." Chao at 195. This process identified some potential new onset cases among the unvaccinated people. However, researchers did not review medical records of unvaccinated people. Id. Instead, "Rubin's multiple imputation was used to estimate the rates of new-onset autoimmune conditions by treating the actual status of new onset as missing data for the un-reviewed potential cases." Id.

The two steps of not reviewing medical records and using Rubin's multiple imputation generated a large amount of testimony from Dr. Zizic and Dr. Rose. Dr. Zizic and Dr. Rose agreed that although Rubin's imputation might be used when data is missing, the data was not missing. The researchers could have

accessed the medical records of the non-vaccinated people. Tr. 368-69, 372, 376, 416, 424-27, 568-69.[8]

Having determined the incidence of SLE in vaccinated people and having estimated the incidence of SLE in unvaccinated people, the researchers compared the rates. The researchers conducted a main comparison and two sensitivity analyses. Tr. 428. The results are presented in Table 3. Chao at 199, Tr. 427.

The incident rate ratio ("IRR") was relatively close to 1.0 for all three situations (1.07, 1.26, and 1.10).[9] These rates and other data led the researchers to conclude: "There was no clear evidence of safety signal for autoimmune conditions following vaccination with HPV4 in this study." Chao at 201. In doing so, the researchers recognized three limitations: (1) a potential complication for determining the onset of a disease, (2) many autoimmune diseases involved small numbers of cases, limiting the study's power, and (3) the multiple imputation method was not a standard method for estimating background incidence rates. Id. at 201-02, accord Tr. 731.

Dr. Zizic criticized the methodology in a few respects. First, he did not agree with limiting the risk period to 180 days. His point that some autoimmune diseases such as lupus could take longer than six months to recognize is a fair one. However, the researchers attempted to design a study to account for any potential delay in diagnosis. Moreover, Dr. Zizic has not presented any opinion to explain why any delay in diagnosis would skew the results. It would seem that because the researchers used the same algorithm to find autoimmune diseases in the vaccinated and unvaccinated groups, any flaw would not make a difference.

Second, Dr. Zizic criticized the researchers for using Rubin's imputation. This criticism has some validity as the researchers acknowledged if "the true new-onset confirmation rate was lower in the unvaccinated population, this may have biased the IRR estimates." Chao at 202. But, again, Dr. Zizic fails to show why this unusual methodology skewed the results. In this regard, Dr. Zizic had a challenging task because some of the work of Chao and colleagues appears

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[8] Dr. Rose speculated that researchers did not have sufficient staffing to review all charts of unvaccinated people. Tr. 427, 568. Dr. Zizic considered a lack of resources to be "absurd." Tr. 732.

[9] An incidence rate ratio above 1.0 suggests that an agent may have caused a disease. See In re Viagra Products Liability Litigation, 572 F.Supp.2d 1071, 1078 (D. Minn. 2008).

undisclosed. Dr. Zizic challenges the way the researchers determined an estimated number of cases in the unvaccinated, reflected in Table 3 as 58 cases or an incidence of 10.3 per 100,000 person-years. Tr. 376, 733. In Dr. Zizic's view, because the case review committee confirmed systemic lupus erythematosus in only one-third of the potential cases, then the incidence rate should be one-third lowered in the unvaccinated group.

Dr. Zizic's criticism is unpersuasive. First, how the researchers determined the estimated number of cases is not well-explained. Dr. Zizic seems to assume that the 58 cases correspond to data presented in column C of Table 1, a spot at which the CRC confirmed the diagnosis. However, it seems more likely that the Rubin's method was substituted for the CRC review, meaning 58 cases actually corresponds to column E in Table 1. The researchers did not provide how many cases the computer algorithm identified before the researchers used Rubin's method. But, strictly mathematically, if the computer algorithm had identified 174 potential onset cases, then the reduction from potential cases to confirmed cases would have been proportional.

In short, although Dr. Zizic answered a leading question from Ms. Stricker's counsel with an assent that he believed the Chao researchers "messed with" the background rates, Dr. Zizic has not shown this persuasively. Cf. J.C. Equipment Corp. v. England, 360 F.3d 1311, 1315 (Fed. Cir. 2004) (noting that expert testimony based upon leading questions can be rejected).

2. Arnheim-Dahlström

Researchers from Denmark and Sweden investigated whether the qHPV vaccine increases rates of adverse events. Arnheim-Dahlström at 1. "Sweden and Denmark keep population based healthcare registers and thereby have unique opportunities to address the safety of HPV vaccination." Id. at 2, accord Tr. 405. Researchers learned when young women received an HPV vaccine. Arnheim-Dahlström at 2. They also determined when each person experienced a "serious adverse outcome event," defined as "records of inpatient admissions and hospital outpatient and emergency department visits." Arnheim-Dahlström at 3, accord Tr. 407.

The way the researchers collected cases was attacked by Dr. Zizic. Tr. 382–89. To Dr. Zizic, a focus on hospitalizations is not appropriate for SLE because less than 5% of patients with lupus are hospitalized. Tr. 383.[10]

Dr. Rose persuasively countered that pediatric rheumatologists in Europe see their patients in hospitals. Tr. 407, see also Arnheim-Dahlström at 5. Thus, the methodology in Arnheim-Dahlström is reliable.

Arnheim-Dahlström and colleagues looked for serious adverse events within 180 days of vaccination. Arnheim-Dahlström at 3. "This period was chosen to allow for the insidious onset of the diseases studied and because diagnostic investigations may take time." Id. The researchers determined how frequently SLE developed in unvaccinated and vaccinated people. Arnheim-Dahlström at 8 (Table 2). The adjusted rate ratio was 1.35 with a 95% confidence interval of 0.69-2.67. Arnheim-Dahlström at 10 (Figure 2), accord Tr. 411.

The researchers summarized: "the findings of this study, which were based on nearly one million girls and 700 000 vaccine doses, were reassuring for autoimmune . . . events after qHPV vaccination." Arnheim-Dahlström at 4.

3. Geier

In response to Dr. Rose's cite to Chao, Arnheim-Dahlström, and other epidemiologic studies, Dr. Zizic presented a 2015 article by David A. Geier and Mark R. Geier. Exhibit 75 at 7.[11] Geier and Geier undertook a study to evaluate "the potential for HPV4 vaccination to induce serious autoimmune events." Geier at 1225.

Geier and Geier used the VAERS database as their source of information. Geier at 1226, Tr. 289. They searched for specific diseases including SLE by computer code. Id. For controls, Geier and Geier used other reports from VAERS. Geier at 1226, Tr. 509. Geier and Geier determined the odds ratio for developing SLE after an HPV vaccination was 5.3. Geier at 1228 (Table 2).

The experts took different views about the value of this article. In response to a leading question from Ms. Stricker's attorney, Dr. Zizic indicated that there is nothing wrong from a methodological standpoint. Tr. 355. In contrast, Dr. Rose

[10] Ms. Stricker has not advanced any argument against Arnheim-Dahlström in her posthearing brief.

[11] Ms. Stricker submitted the Geier and Geier article as Exhibit 64. She later resubmitted it as Exhibit 95.

stated that this study is "absolutely not" reliable. Tr. 505. Dr. Rose stated "The definition of exposure is totally biased and bogus. The calculation of controls versus cases is ridiculous." Tr. 509. Dr. Moy raised additional concerns. Tr. 671-74.

Ms. Stricker has not established the reliability of this Geier and Geier article. A primary flaw is using the VAERS database as a source. In multiple cases, special masters have rejected this methodology.[12] See Tompkins v. Sec'y of Health & Hum. Servs., 117 Fed. Cl. 713, 721 (2014) (quoting special master's decision describing the VAERS database as a "stocked pond"); Analla v. Sec'y of Health & Hum. Servs., 70 Fed. Cl. 552, 558 (2006) (noting that the Court has uniformly upheld concerns of special masters about VAERS reports); see also Doe v. Ortho-Clinical Diagnostics, Inc., 440 F.Supp.2d 465, 475-76 (M.D.N.C. 2006) (noting that Dr. Geier's use of VAERS reports was not reliable).

In their article, Geier and Geier attempted to vouch for their methodology by asserting the "VAERS Working Group of the CDC and the FDA have repeatedly analyzed and published epidemiologic studies based upon VAERS [6, 7]." Geier at 1226. Reference 7 is a 2002 article by the Geiers, which does not support a statement that the CDC used the VAERS database for an epidemiologic study. Tr. 508. In addition, Dr. Rose stated that the other reference by Singleton is not an epidemiologic study. Tr. 507.[13]

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[12] In a hearing before the Chief Special Master on October 22, 2021, Dr. Zizic was told that the Geiers are not trustworthy. See Chambers v. Sec'y of Health & Hum. Servs., No. 19-140V, 2022 WL 3369332, at *10 n.15 (Fed. Cl. July 22, 2022) ("the Geiers have repeatedly, and over a lengthy period of time, been deemed to be questionably-competent and scientifically-unreliable experts in the Vaccine Program—casting significant doubt on any studies they have authored."). The Chambers hearing took place after the March 4, 2019 submission of Dr. Zizic's report and the Geier article; however, Dr. Zizic still stated that Geier was "not a flawed study" in the January 2022 hearing in the instant case. Dr. Zizic was asked about the instruction in Chambers but did not recall the Chief Special Master telling him this. Tr. 288-89. Regardless of Dr. Zizic's knowledge about the Geiers, the Geiers' work is problematic.

[13] Because Dr. Rose consulted and testified about Singleton, the better practice would have been to disclose this opinion and to file the Singleton article. However, in light of the consistent rejection of work by the Geiers, this oversight is harmless.

Furthermore, Geier and Geier have been repeatedly discredited in the Vaccine Program. See, e.g., America v. Sec'y of Health & Hum. Servs., No. 17-542V, 2022 WL 278151, at *8 n.16 (Fed. Cl. Jan. 4, 2022) ("the authors of the Geier Article have been almost wholly discredited as experts in the Vaccine Program.") (citing Hooker v. Sec'y of Health & Hum. Servs., No. 02-472V, 2017 WL 3033940, at *17 (Fed. Cl. Spec. Mstr. Apr. 11, 2017); King v. Sec'y of Health & Hum. Servs., No. 03-584V, 2011 WL 5926126, at *15 (Fed. Cl. Sept. 22, 2011) Doe/03 v. Sec'y of HHS, 2007 WL 2350645, at *3 (Fed. Cl. Spec. Mstr. July 31, 2007); and Daly v. Sec'y of HHS, No. 90–590V, 1991 WL 154573, at *7 (Cl. Ct. Spec. Mstr. July 26, 1991)). Thus, although the Geier article has been considered, it carries minimal weight.

4. Wang

About one week before the hearing, Ms. Stricker submitted a 2017 article by Bin Wang and others.[14] Dr. Zizic did not recall when he learned of the Wang article. Tr. 320. Wang and colleagues investigated whether vaccines increased the rate for developing SLE and rheumatoid arthritis. Wang at 756.

The researchers' methodology was to perform a meta-analysis. Tr. 180, 205.[15] Wang and colleagues searched various databases for defined observational studies. Wang at 757. From a group of studies, the researchers selected some based upon various criteria, one of which was that the study's "controls were those individuals without receiving vaccination." Id. The authors also assessed the studies for quality (bias). Id. From the accepted studies, the authors extracted data and pooled them. Id., Tr. 205.

The authors represented that the "present meta-analysis was performed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement." Wang at 757. To Dr. Zizic, a study done in conformance with PRISMA's methodology enhances its credibility. Tr. 207, 289.[16] Nevertheless, Dr. Rose questioned the extent of peer review. The article indicates

[14] Arguably, the submission of an article without an accompanying disclosure from an expert was not in accordance with the January 29, 2020 order for briefs. However, the Secretary did not object.

[15] At line 5 of transcript page 180, "Lane" should be "Wang."

[16] The PRISMA website indicates "PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review." http://www.prisma-statement.org/.

that the journal that published the article, Autoimmunity Reviews, received a manuscript on April 19, 2017. Wang at 756. The article was accepted on April 23, 2017 and available online May 5, 2017. Id. Dr. Rose wondered how the peer-review could have worked in just four days. Tr. 497-98. Dr. Rose also asserted that the editors-in-chief of Autoimmunity Reviews are Dr. Shoenfeld and Dr. Gershwin, who have frequently testified that a vaccine injured someone. Id.

Overall, the researchers identified five studies involving the HPV vaccine and SLE. Wang at 760 (Table 3), Tr. 287. These relevant five studies were by Verstraaten, Chao, Arnheim-Dahlström, Angelo, and Geier. Tr. 499; see also Wang at 759 (Table 1).

The Geier study used in Wang was published in 2017 and is reference 48 in the Wang article. The 2017 Geier article is not an exhibit in this case. The 2015 Geier article, which is Exhibit 64 and Exhibit 95, is reference 60 in Wang. The Wang group excluded the 2015 Geier article because its data was "overlapping." Wang at 758.

Including the Geier study in the Wang meta-analysis is both questionable and significant. As discussed, the methodology of Geier and Geier is not reliable. Although Wang and colleagues assessed Geier and Geier as having high quality, Dr. Rose noted that Geier and Geier did not deserve a high ranking because they could not verify the outcome through the VAERS reports. Tr. 500.

Including the 2017 Geier study affected the results in Wang. Tr. 290, 504. Of the five relevant studies, the Geier study found the highest relative risk. Wang at 760 (Figure 2) (highlighting added to identify studies involving the HPV vaccine). Geier is the only article in which the 95% confidence interval did not cross 1.0. See Id., Tr. 504.

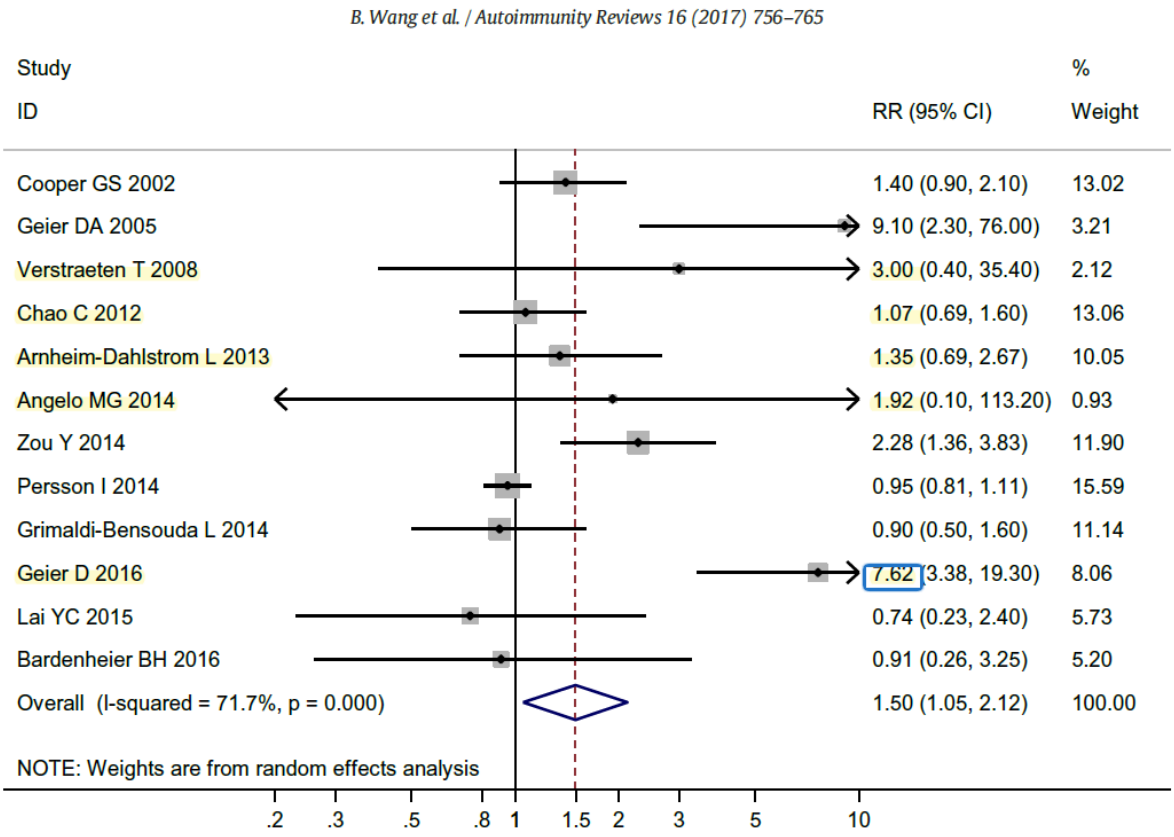

Fig. 2. Meta-analysis of 12 eligible studies showed that vaccinations significantly increased risk of SLE.

Accordingly, the Wang article merits little, if any, weight. Cf. Moran v. Sec'y of Health & Hum. Servs., No. 16-538V, 2021 WL 4853544, at *29 (Fed. Cl. Spec. Mstr. Oct. 4, 2021) (giving less weight to the Wang study in the context of a claim that influenza vaccination caused rheumatoid arthritis).

5. Miranda

Among the exhibits in this case, the next epidemiologic study chronologically was written by Sara Miranda and other researchers from France. This study was not included in the Wang meta-analysis.

This group also used computer searches to determine whether the HPV vaccination was associated with various autoimmune diseases, including SLE. Miranda at 4761. In France, two nationwide databases linked by unique individual identifiers collect health information of the populace. In these databases, the researchers generally looked for any women aged 13-16 years from January 1, 2008 through December 31, 2012. Miranda at 4762. More than 2 million young women were followed for an average of 33 months. Miranda at 4763. The researchers attempted to find out when these people experienced 14 autoimmune

diseases including SLE. The researchers searched for ICD-10 codes, long-term reimbursement records, and marker drugs. Miranda at 4762 (section 2.4).

Dr. Zizic, Dr. Rose, and Dr. Moy had different opinions as to the soundness of this methodology. In his oral testimony, Dr. Zizic presented Supplemental Table 1. This supplemental table shows that no marker drugs were associated with SLE. Tr. 723. Dr. Zizic also maintained that the researchers would not capture the "vast majority of lupus cases" because people with lupus are rarely hospitalized. Tr. 724. He estimated one in 10,000 cases of lupus would be hospitalized. Tr. 723. In contrast, Dr. Rose and to a lesser extent Dr. Moy defended the methodology. The researchers also look at "long-term illness reimbursement records." Miranda at 4762. These records, according to Dr. Rose and Dr. Moy, would identify people suffering from SLE because SLE is a chronic disease. Tr. 438, 693-94, 757. Dr. Zizic did not refute the point regarding reimbursement records for long-term illnesses.

Dr. Zizic's criticisms were further undone by the results in Miranda. Miranda and colleagues identified 184 patients with lupus. Miranda at 4764 (Table 3). Among the unvaccinated, 139 cases of lupus were found with an incidence rate of 3.42. Id. Among the vaccinated, 45 cases were found with an incidence rate of 3.23. Id. When these numbers were pointed out to Dr. Zizic, he conceded the authors' ability to detect cases in either group would be the same. Tr. 749.

Having determined the incidence rate for cutaneous or systemic lupus erythematosus among the unvaccinated vaccinated populations,[17] the researchers determined a hazard ratio ("HR").[18] The unadjusted hazard rate was 0.97 with a

[17] A less significant criticism from Dr. Zizic was combining cutaneous lupus with systemic lupus erythematosus. Tr. 723. But, this contention was easily countered by Dr. Rose, who opined without contradiction that SLE is much more common. Tr. 438-39.

[18] "A hazard ratio is used in epidemiological studies to compare two populations with hazard functions by dividing the risk of a particular event by the baseline risk. Gerald Van Belle, Statistical Rules of Thumb, 130 (2nd ed. 2008). If the hazard ratio is less than one, the second group is less affected than the first. Stanton Glantz, Primer of Bio-statistics, 388 (4th ed. 1997). If the hazard ratio is greater than one, the second group is more affected than the first. Id. If the hazard ratio is one, the groups are affected at equal rates. Id." Spahn v. Sec'y of Health & Hum. Servs., No. 09-386V, 2014 WL 12721080, at *11 n.17 (Fed. Cl. Sept. 11, 2014), mot. for rev. denied, 133 Fed. Cl. 588, 603 (2017).

95% confidence interval of 0.67-1.39. Miranda at 4764 (Table 3). The adjusted hazard rate was minimally increased: 1.01 (95% CI: 0.69-1.48). Miranda at 4765 (Figure 1).

The authors concluded: "our study provides reassuring results with respect to the risk of AID after HPV vaccination, confirming the results of previous epidemiological studies." Miranda at 4767.

6. Liu

Dr. Rose also cited a 2018 study by Karen Liu and others. Exhibit T. This article was not included in the Wang meta-analysis. Tr. 498. These researchers used databases from Ontario, Canada. "The study cohort consisted of 290 939 girls aged 12-17 years who were eligible for vaccination between 2007 and 2013." Liu at E648; accord Tr. 470. After determining when the young women received and HPV vaccine, researchers focused on illnesses appearing within sixty days of the vaccination. Liu at E650.

In Dr. Zizic's report, he criticized the use of a 60-day window, although Dr. Zizic did not testify about Liu orally. Dr. Rose stated a risk period of 60 days more likely conforms to what is biologically plausible. Tr. 471. Dr. Rose also pointed out that the authors expended the window in a sensitivity analysis to 180 days. Liu at E650. The authors stated this study "had more than 90% power to detect a rate ratio of 2.0 for autoimmune disorders." Id.

For "systemic autoimmune rheumatic diseases," the adjusted rate ratio was 1.21 with a 95% confidence interval of 0.57-2.57. Liu at E653 (Figure 3), Tr. 472. The category of systemic rheumatic diseases includes systemic lupus erythematosus, system sclerosis, Sjorgen's syndrome, dermatomyositis, and polymyositis. Liu at E653 (Figure 3: caption). Dr. Rose persuasively explained why including other diseases with SLE would not affect the analysis. Tr. 472.

The authors concluded: "This large population-based study did not find a significant risk of autoimmune disorders following HPV4 vaccination among girls aged 12-17 years. . . . These findings add to the growing body of evidence on the safety of this vaccine." E654.

7. Jorgensen

With Ms. Stricker's Prehearing Reply, filed on July 22, 2020, she submitted an article written by Lars Jorgensen and others published in 2020. Exhibit 82. The researchers gained access to 79% of clinical study reports, which underlie the

report of HPV vaccine safety that the vaccine manufacturer submitted to European regulatory agencies. Jorgensen at 3, Tr. 245-47.

After gathering these clinical safety reports, the authors extracted some data and conducted a meta-analysis. In doing so, Jorgensen and colleagues focused on various outcomes. Jorgensen at 3. This list did not include lupus. Tr. 317-19.

The researchers concluded that the manufacturer's safety studies contained a "high risk of bias." Jorgensen at 7. The reason for bias was that nearly all controls "received an active comparator such as HPV vaccine aluminum-containing adjuvants." Id. Dr. Zizic explained that the controls did not receive a placebo. Instead, the controls, like the vaccinated populations, received an adjuvant. Tr. 248-49, see also Tr. 316 (Dr. Rose). The authors suggested that for some conditions (but not lupus), HPV vaccines may cause more harm than previously reported. Jorgensen at 15.

Due to the relative newness of the Jorgensen study, the undersigned submitted an article about Jorgensen before the hearing. Order, issued January 10, 2022, see also Tr. 703-04. This author opined that Jorgensen "demonstrates the risk of relying too much on CSR's [clinical study reports]." Bastian at 41. Dr. Zizic described Bastian's comments as "unsubstantiated." Tr. 250.

Further assessment of the details of Jorgensen and Bastian's criticism is not required. Jorgensen did not provide any information helpful to determining whether HPV vaccines can cause SLE. See Tr. 317-19.

8. Grimaldi-Bensouda

Dr. Rose presented a different type of study by Grimaldi-Bensouda and others, published in 2016. The source of information was a French database, known as the PGRx autoimmune disease study group. Tr. 549. Board-certified specialists place information about people with autoimmune diseases into the database and general practitioners refer other people who can act as controls. Grimaldi-Bensouda at 83. The methodology was to find people with a disease and then look backwards to see if a person with the disease had been vaccinated. Tr. 549. SLE was a disease of interest. Grimaldi-Bensouda at 85 (section 2.2); Tr. 551. The crude odds ratio for SLE was 0.78 with a 95% confidence interval of 0.40-1.52. Grimaldi-Bensouda at 85 (table 2), Tr. 550.[19]

[19] Dr. Rose appears to discuss the odds ratio for all autoimmune diseases when he describes the odds ratio as 0.58. See Grimaldi-Bensouda at 85.

The authors concluded: "the ongoing surveillance of HPV vaccination using the PGRx information system showed no increased risk of ADs [autoimmune diseases] among young females." Grimaldi-Bensouda at 89; accord Tr. 550-51.

9. Summary

The reliable controlled studies do not support a finding that an HPV vaccine can cause systemic lupus erythematosus. Four studies (Chao, Arnheim-Dahlström, Miranda, and Liu) did not detect an increased incidence of SLE following HPV vaccination. The study populations were large---more than one hundred thousand people in each of the four studies and more than two million people in Arnheim-Dahlström and Miranda.

Ms. Stricker attempted to undermine the methodologies. However, she failed to show any significant flaw for Arnheim-Dahlström, Miranda, or Liu. Their methods appear reliable and the conclusions that the HPV vaccine does not increase the incidence of SLE are fair. For Chao, the evidence regarding methodology is mixed. Ms. Stricker can legitimately point to a non-standard technique for filling in missing data, which was not really missing. But even if Chao were excluded, the Arnheim-Dahlström, Miranda, and Liu articles still indicate that researchers have not detected an increased incidence.

The only researchers to purport to detect an increased incidence are Geier and Geier. However, their methodology is suspect, and any results are not reliable. This rejection of Geier and Geier causes a corresponding rejection of Wang.

The Grimaldi study, which approached the question of whether an HPV vaccination is safe from a different perspective, tends to corroborate the findings of Chao, Arnheim-Dahlström, Miranda, and Liu. Although this study is smaller (involving approximately 2,300 people), HPV vaccination was not statistically associated with SLE.

B. Studies on the Effect of Vaccination

The next type of study concerns how vaccines affect people. Ms. Stricker introduced two articles on this topic, one by M. Abu-Shakra and the other by Natasha Toplak. The Secretary presented one by J. Patricia Dhar.

In the 2002 Abu-Shakra study, the researchers gave 24 women with SLE a flu vaccine. Abu-Shakra at 369, Tr. 489. The researchers found that various antibodies, including antibodies associated with lupus, increased 6 and 12 weeks after the vaccination. Abu-Shakra at 370-71, Tr. 191-92.

While the levels of antibodies changed, "the generation of anti-ENA [extractable nuclear antigen] was not associated with a specific clinical response." Abu-Shakra at 372; accord Tr. 192-93. The researchers also noted "we have shown [in a different paper] that influenza virus vaccine is safe for patients with SLE." Abu-Shakra at 371; accord Tr. 489. In the present paper, Abu-Shakra concluded: "Patients with SLE should be encouraged to receive the influenza vaccine." Abu-Shakra at 372.

Dr. Zizic stated that he would not conclude the flu vaccine was safe. Tr. 193. To him, the antibodies that were produced after vaccination would cause damage. Tr. 192. The patients in the Abu-Shakra study did not have adverse consequences because, according to Dr. Zizic, they were being treated for lupus. Tr. 193. When asked about the people in Abu-Shakra receiving a flu vaccine versus the HPV vaccination that Ms. Stricker received, Dr. Zizic's response was the HPV vaccine is the "same difference." Tr. 194, accord Tr. 327. On the other hand, Dr. Rose harmonized the increase in antibodies and the lack of clinical manifestations differently. Dr. Rose stated that fluctuations in antibodies do not mean much. Rheumatologists care about only a few antibodies that might correlate to disease severity. Tr. 492-93.

Next, Natasha Toplak and colleagues conducted a somewhat similar experiment, which was reported in 2008. The researchers gave flu vaccine to 92 "apparently healthy adults." Toplak at 135. Although the researchers described them as "apparently healthy," Dr. Rose pointed out that a large fraction (24%) tested positive for ANA antibodies before the vaccination. Tr. 486; see also Toplak at 136 (Table 1). The researchers determined the number of volunteers who tested positive for antibodies before the vaccination, one month after the vaccination, and six months after the vaccination. Toplak at 136, Tr. 485. Some people experienced an increase in antibodies. Toplak at 136. The authors did not show how much any antibody increased. Tr. 487. The authors did not present any controls, meaning people who were not vaccinated. Tr. 488.

Dr. Rose orally testified that this paper did not show anything of significance. Tr. 486-87. Dr. Zizic barely mentioned Toplak in his oral testimony. Tr. 327.

A third study was reported by J. Patricia Dhar in 2017. Exhibit W. Dr. Rose described it as a "clinical trial." Tr. 553. In this study, 34 "women ages 18-50 years with a history of mild to moderate SLE (and no other autoimmune disease) and minimally active or inactive SLE volunteered to participate in the study." Dhar at 2643; accord Tr. 553. The participants were all vaccinated with the qHPV

Gardasil vaccine. Dhar at 2642. The researchers determined whether the subjects experience an SLE flare.

The researchers found "no instance of SLE flare." Dhar at 2645. Dr. Rose interpreted this finding as "indirect evidence that [HPV vaccination is] not related to at least the mechanism of lupus exacerbation." Tr. 554.

Overall, these types of studies do not meaningfully support Ms. Stricker's claim that the HPV vaccine can cause SLE. She submitted two articles which are at least one step removed from situation in that Abu-Shakra and Toplak studied the flu vaccine, not the HPV vaccine. More importantly, neither Abu-Shakra nor Toplak showed the people with SLE who received the flu vaccine got worse. This lack of worsening was also evident in Dhar, which involve the HPV vaccine. If the HPV vaccine were causing a worsening of disease, then the results could have appeared in Dhar.

C. Case Reports / Case Series

Another type of evidence is either a case report or a case series. See Tr. 512 (defining a "case series" as an article with more than one case report). Ms. Stricker contributed two: articles by HF Soldevilla and Mariele Gatto. Dr. Zizic testified orally about Gatto but not much about Soldevilla. See Tr. 199-202.

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).[20]

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. Recent 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).

Testimony from Dr. Rose and Dr. Moy confirms that case reports are generally not effective ways to show causation. Tr. 512, 669-71. There are

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

additional problems with Soldevilla and with Gatto. Dr. Moy criticized Soldevilla and Gatto for their lack of controls, unclear diagnoses, and inferences drawn from temporal proximity. Tr. 512-16. He did not think these cases were reliable, or representative of Ms. Stricker's case. Id. Likewise, Dr. Rose testified that neither Soldevilla nor Gatto established causation, and criticized their reliance on temporal association. Tr. 670-71; see also Exhibit L at 20-21. Accordingly, although the case reports have been considered, they are given little weight.

Overall, the studies submitted by the parties tend to undermine a claim that the HPV vaccine can cause SLE. However, these studies cannot prove a negative. Therefore, the theories Ms. Stricker presented are addressed next.

D. Theories

Ms. Stricker proposed two theories by which HPV vaccine can cause SLE. The theory that received the most attention, by far, was molecular mimicry. The other less prominent theory involved Granzyme B.

1. Molecular Mimicry

Because special masters are often called upon to evaluate the persuasiveness of the theory of molecular mimicry, the Court of Federal Claims and the Court of Appeals for the Federal Circuit have considered molecular mimicry in their appellate role. In December 2019, the undersigned identified the leading precedents as W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352 (Fed. Cir. 2013), and Caves v. Sec'y of Dep't. of Health & Hum. Servs., 100 Fed. Cl. 119 (2011), aff'd sub nom., 463 F. App'x 932 (Fed. Cir. 2012). Tullio v. Sec'y of Health & Hum. Servs., No. 15-51V, 2019 WL 7580149, at *12-14 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), mot. for rev. denied, 149 Fed. Cl. 448 (2020). While Tullio describes those cases in more detail, their essence appears to be that although molecular mimicry is accepted in some contexts, special masters may properly require some empirical evidence to show that a particular vaccine can cause a particular disease.

In the next approximately three years, appellate authorities reviewing decisions involving molecular mimicry have generally endorsed the approach of looking for some evidence that persuasively shows that a portion of a vaccine resembles a portion of human tissue, which contributes to causing the disease, and

that the immune system will respond to the relevant amino acid sequence.[21] Chronologically, the list of more recent appellate cases begins with the opinion in Tullio, which denied the motion for review. 149 Fed. Cl. 448, 467-68 (2020).

Another example in which the Court of Federal Claims held that the special master did not elevate the petitioner's burden of proof in the context of evaluating the theory of molecular mimicry is Morgan v. Sec'y of Health & Hum. Servs., 148 Fed. Cl. 454, 476-77 (2020), aff'd in non-precedential opinion, 850 F. App'x 775 (Fed. Cir. 2021). In Morgan, the Chief Special Master found that petitioner had not presented persuasive evidence about a relevant antibody. Id. at 477. The Chief Special Master also noted that the articles about the relevant disease do not list the wild flu virus as potentially causing the disease. Id. When examining this analysis, the Court of Federal Claims concluded: "the Chief Special Master did not raise the burden of causation in this case; petitioner simply failed to meet it." Id.

The Federal Circuit also evaluated the Chief Special Master's approach in Morgan. The Federal Circuit concluded: "We discern no error in the special master's causation analysis." 850 F. App'x 775, 784 (Fed. Cir. 2021).

Most other recent appellate cases follow this path. See, e.g., Duncan v. Sec'y of Health & Hum. Servs., 153 Fed. Cl. 642, 661 (2021) (finding the special master did not err in rejecting a bare assertion of molecular mimicry); Caredio v. Sec'y of Health & Hum. Servs., No. 17-79V, 2021 WL 6058835, at *11 (Fed. Cl. Dec. 3, 2021) (indicating that a special master did not err in requiring more than homology and citing Tullio); Yalacki v. Sec'y of Health & Hum. Servs., 146 Fed. Cl. 80, 91-92 (2019) (ruling that special master did not err in looking for reliable evidence to support molecular mimicry as a theory); but see Patton v. Sec'y of Health & Hum. Servs., 157 Fed. Cl. 159, 169 (2021) (finding that a special master erred in requiring petitioner submit a study to establish medical theory causally connecting flu vaccine to brachial neuritis).

A foundation for the molecular mimicry theory in this case is a belief that the development of lupus requires both a genetic disposition and an environmental factor. See Doria at 25. Infections such as from viruses have been proposed as

[21] The term "homology" is used when discussing molecular mimicry. "Homology" is defined as "the quality of being homologous; the morphological identity of corresponding parts; structural similarity due to descent from a common form." *Dorland's* at 868.

potential triggers. Rose at 381. The Epstein-Barr virus has been theorized as one agent contributing to the pathogenesis of SLE. Doria at 25, Tr. 184.

The basic theory of molecular mimicry is that some components of an antigen resemble a human being's own tissue. This concept is called "homology." A person's immune system cross-reacts and mistakenly targets the host's tissue.

An article Dr. Zizic introduced, Kanduc, demonstrated that viruses and people have extensive homology. Kanduc at 1396, Tr. 461. Kanduc suggested that the commonness of homology undermines the idea that viral infections lead to autoimmune disease. Tr. 461; but see Tr. 312-13, 785-87. Kanduc commented that after "three decades of intensive research in the field, a causative link between molecular mimicry and human autoimmune disease is still sub judice and the molecular mimicry hypothesis has received no validation." Kanduc at 1395. With respect to this commentary, Dr. Rose rhetorically asked: "if there is no proof, why should we accept [molecular mimicry] as happening in this case?" Tr. 463.

Although Dr. Zizic testified in rebuttal, Dr. Zizic did not effectively answer Dr. Rose's question. However, earlier, Dr. Zizic put forward the Segal article as supporting molecular mimicry.

To support the theory that the HPV vaccine has homology with parts of the human body involved in SLE, Dr. Zizic heavily relied upon a 2017 article by Yahel Segal, Yehuda Shoenfeld, and others. See Tr. 194-99. These researchers searched databases containing the amino acids sequences of the HPV L1 protein, which is part of the HPV vaccine, and "human proteins that when altered, are associated with SLE." Segal at 567; accord Tr. 454. The authors presented their findings in Table 1, which received much attention during the hearing.

In Dr. Zizic's view, "a multiplicity of pentapeptides shared by the herpes papillomavirus of the same strains that are in the vaccine that end up causing the functional problems that lead to autoimmune disease particularly lupus in these patients." Tr. 198. He concluded "the diseases on the right hand side [of Table 1] are resulting from the proteins that are involved in lupus that are peptide sharing with the virus." Tr. 199. Contrastingly, Dr. Rose indicated the findings had more limited significance. When asked on cross-examination whether "Table 1 reflects identity homology between the HPV L1 capsid protein and various host tissue known to be amino pathogenic for lupus," Dr. Rose responded, "the word amino pathogenic is not correct." Tr. 595. Dr. Rose distinguished between autoantibodies that are "associated with" lupus and autoantibodies that could be pathogenic. Tr.

595-96. Dr. Rose went on to assert that labeling a column in Table 1 as SLE-associated proteins is "misleading." Tr. 597.

In rebuttal, Dr. Zizic did not persuasively counter Dr. Rose's point regarding (the lack of) proof for pathogenesis. Discussing peptides that are part of complement, Dr. Zizic stated an antibody's attack on complement could interfere with the complement system and end up causing lupus. But, according to Dr. Zizic, "we can't prove that. All I'm saying is there's great biologic plausibility." Tr. 735. Dr. Zizic stated "it is very conceivable… If you form an antibody against the components of complement, they can no longer fit in the complement cascade… And end up with autoimmune disease, including lupus." Tr. 736.

In addition to questioning the pathological relevance, Dr. Rose raised a second point. Dr. Rose also opined that any pentapeptides listed in Table 1 "has to be antigenically relevant, meaning that they have to be able to generate antibodies." Tr. 455-56, accord Tr. 518, 764. The pentapeptide's ability to lead to a production of antibodies depends, in part, on its location in a cell. Tr. 456. Dr. Zizic did not persuasively rebut Dr. Rose's point.

In short, Dr. Rose's interpretation of the Segal paper hits the target. Any statement that antibodies to specific proteins cause lupus would exaggerate what is known. See A.F. v. Sec'y of Health & Hum. Servs., No. 19-466V, 2023 WL 251948, at *25 (Fed. Cl. Spec. Mstr. Jan. 18, 2023) (indicating that a different paper by Segal and Shoenfeld offered homology based on "non-substantiated contentions about amino acid sequencing"). The triggers for lupus are not known. Tr. 306 (Dr. Zizic), 404 (Dr. Rose); see also Parks (exhibit H). Accordingly, while Segal and others have identified homologous sequences of five amino acids, there has not been any persuasive showing that an attack on these pentapeptides would cause lupus. The finding of pentapeptide similarity might be enough to generate some interest to conduct more experiments. Tr. 458; see also Tr. 595 (describing homology as "one step"), Tr. 765 (describing Kanduc as the first step).

Stating that the evidence in this case is insufficient to credit molecular mimicry as a theory by which HPV vaccine can cause SLE is not the same as requiring scientific certainty. Petitioners do not need to prove causation beyond a reasonable doubt. Petitioners need only evidence that preponderates. Zatuchni v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 612, 622 (2006). However, many appellate cases have sustained decisions by special masters that rejected molecular mimicry. See, e.g., Morgan, 850 F. App'x 775 (Fed. Cir. 2021); Duncan, 153 Fed. Cl. 642 (2021); Yalacki, 146 Fed. Cl. 80 (2019). So, too, in this case, Ms. Stricker has failed to meet her burden of proof.

2. Granzyme B

Ms. Stricker may have presented a second theory involving Granzyme B and defective clearance. See Tr. 168, 259-65, Petitioner's Posthear'g Br. at 56-57; But see Pet'r's Posthear'g Br. at 29 ("Dr. Zizic's expert medical theory is based upon molecular mimicry"). However, this theory has been confusing for a long time. Although Dr. Zizic mentioned defective cell clearance in his first report (Exhibit 37 at 31), the undersigned commented in the March 12, 2019 status conference that the theory was not explained well. In the intervening years, Ms. Stricker and Dr. Zizic have not submitted evidence clarifying the theory.

Whether Granzyme B and/or defective cell clearance might contribute to the cause of systemic lupus erythematosus is debatable. However, the details of arguments can be set aside for a more fundamental reason. Even if Granzyme B and/or defective cell clearance were a part of the pathogenesis for SLE, Ms. Stricker has not connected the HPV vaccine to Granzyme B and/or defective cell clearance. The lack of connection is most notable in the section of Ms. Stricker's posthearing brief on defective cell clearance and Granzyme B. Over the course of one and one-half pages here, Ms. Stricker does not mention the HPV vaccine at all. She also does not return to defective cell clearance and/or Granzyme B in her posthearing reply. On cross-examination, Dr. Zizic admitted Granzyme B "has nothing to do with infection or vaccination." Tr. 297. Accordingly, Ms. Stricker has failed to demonstrate how a theory involving Granzyme B and/or defective cell clearance explains how the HPV vaccine can cause SLE.

E. Summary on Theory

As discussed, the primary theory by which Ms. Stricker attempts to show a way by which the HPV vaccine can cause SLE is molecular mimicry. However, the evidence, considered as a whole, is lacking. Large-scale epidemiologic studies involving millions of people have not detected an increased incidence of SLE following the HPV vaccination. The Dhar study, which involved fewer than 100 people, indicated that people with SLE can receive the HPV vaccine without worsening their disease. The article most directly discussing molecular mimicry in the context of the HPV vaccine and SLE (Segal) lacks persuasive value. None of these points is dispositive by itself. But, taken as a whole, the evidence does not support a finding that the HPV vaccine can cause SLE.

A finding that Ms. Stricker has failed to meet one of the Althen prongs means that she is not entitled to compensation. Nevertheless, the additional Althen prongs are reviewed for completeness, although they are taken out of order.

V. Althen Prong 3

The third Althen prong requires "a showing of 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).

Dr. Moy proposed that if HPV vaccine can cause SLE, then a medically appropriate interval is 4 to 6 weeks. Exhibit A at 6. For Ms. Stricker, Dr. Moy's definition means the SLE must have begun to manifest between October 27, 2015 and November 10, 2015. Resp't's Posthear'g Br. at 24.

Although the Secretary contends Ms. Stricker's lupus was not apparent until November 26, 2015 (Resp't's Posthear'g Br. at 25), persuasive evidence shows that the onset was on approximately November 1, 2015. Thus, if molecular mimicry had been accepted as a reliable theory in the context of HPV vaccines causing SLE, then Ms. Stricker could have met her burden on prong three.

A finding that a vaccinee's disease began shortly after vaccination is not a sufficient basis to find causation. Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144 (Fed. Cir. 1992) ("Temporal association is not sufficient, however, to establish causation in fact."). In addition to presenting a sequence of events, Ms. Stricker is obligated to present a causal theory and to show a logical sequence of cause and effect. For the reasons, explained above in Section IV, Ms. Stricker did not meet her burden regarding theory. Whether she meets her burden regarding the second Althen prong is discussed next.

VI. Althen Prong 2

The second Althen prong requires "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. As a matter of logic, when a petitioner fails to meet their burden to show that a vaccine *can* cause an injury, the petitioner also fails to show that a vaccine *did* cause their injury. The lack of evidentiary support for the first Althen prong may be considered in the analysis of the other Althen prongs. See Temes v. Sec'y of Health & Hum. Servs., 151 Fed. Cl. 448, 464 (2020); Caves v. Sec'y of Health & Hum. Servs., 100 Fed. Cl. 119, 145 (2011). However, for sake of completeness,

the evidence on this point is discussed as well.[22] Ms. Stricker's evidence primarily consists of Dr. Zizic's opinion, a letter from her rheumatologist, and a letter from her primary care physician. See Pet'r's Posthear'g Br. at 58-64.

To conclude that the HPV vaccine did cause Ms. Stricker's SLE, Dr. Zizic relies upon the temporal interval. See Exhibit 37 (first report) at 43, Tr. 166. Ms. Stricker declined from being apparently healthy and without signs or symptoms of SLE before the vaccination to developing fatigue and muscle pain in early November.

Otherwise, Dr. Zizic describes a progression of signs and symptoms for SLE. Dr. Zizic's reliance on the temporal sequence is not wrong. Appropriate timing is required in all cases. But, Dr. Zizic does not identify any facts about Ms. Stricker that suggest her lupus was due to the vaccine. See Pet'r's Br. For example, Ms. Stricker emphasizes that her mother's multiple sclerosis makes Ms. Stricker at greater risk for developing an autoimmune disease. Pet'r's Posthear'g Br. at 58, citing Tr. 599 (Dr. Rose's testimony). But, this greater risk does not necessarily mean a greater risk for an adverse reaction to the HPV vaccine.

Dr. Zizic also attempts to rule out other potential causes for Ms. Stricker's lupus. An HPV infection and tetracycline use are discussed below. If, for sake of argument, it is assumed that Dr. Zizic ruled these potential alternative causes out, then Ms. Stricker still must do more to meet her burden under Althen. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1323 (Fed. Cir. 2010).

In addition to Dr. Zizic, Ms. Stricker relies upon letters from two treaters, Dr. Saba and Dr. Robinson. The opinions of treating doctors can be quite probative. Cappizano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). However, the views of a treating doctor are not absolute. Snyder v. Sec'y of Health & Hum. Servs., 88 Fed. Cl. 706, 745 n.67 (2009).

Dr. Saba. Dr. Saba concludes her January 31, 2018 letter by saying the idea that the HPV vaccine caused Ms. Stricker's connective tissue disease was "very possible." Exhibit 22. However, statements from treaters about possibilities provide little, if any, assistance to petitioners who must establish their cases with preponderate evidence. See Paterek v. Sec'y of Health & Hum. Servs., 527 F. App'x 875, 883 (Fed. Cir. 2013) ("testimony that causation was 'not impossible' fails to provide support for causation at all"); Austin v. Sec'y of Health & Hum. Servs., 141 Fed. Cl. 268, 280 (2018) (special master was not arbitrary in not

[22] Evidence regarding alternative causes is discussed below in Section VII.

crediting a statement from a treating doctor who described causation as "possible"); Doe v. Sec'y of Health & Hum. Servs., 19 Cl. Ct. 439, 450 (1990) (a treater's statement that causation was "highly possible" does not assist petitioner in presenting preponderant evidence).

Dr. Robinson. Dr. Robinson is a primary care doctor, not Ms. Stricker's rheumatologist. See Tr. 57. Dr. Robinson stated that based upon the temporal sequence, "it does seem likely that [Ms. Stricker's] autoimmune disease was triggered by the vaccine." Exhibit 23. The testifying experts acknowledged Dr. Robinson's letter. Tr. 238, 621, 696.

The Secretary challenges the letters from the treating doctors because the treaters may not have received Ms. Stricker's "complete medical records," and they may not have "conducted any substantial independent research." Resp't's Br. at 20.[23] Ms. Stricker replied that reviewing complete medical records "has never been a requirement in the Vaccine Program, and Respondent cites to no authority to support this requirement as none exists." Pet'r's Posthear'g Reply at 11. Similarly, according to Ms. Stricker, "treating physicians have no requirement of conducting independent research, as they are not expert witnesses." Id.

Special masters may award petitioners compensation based upon "medical records." 42 U.S.C. § 300aa–13(a)(1). Dr. Robinson's January 9, 2018 letter constitutes a medical record. As such, it constitutes evidence supporting Ms. Stricker's claim.

If Ms. Stricker had established Althen prong one and if alternative causes were ruled out, then Dr. Robinson's letter may have been sufficient to win the case for Ms. Stricker. See Langland v. Sec'y of Health & Hum. Servs., 109 Fed. Cl. 421, 438 (2013) ("Federal Circuit precedent makes it evident that the first prong of Althen must be proven before the opinions of treating physicians may clinch causation under the other prongs"). However, for reasons explained above, Ms. Stricker has not established the first condition – proof on prong 1. As to the second condition – a ruling out of other causes, that question is addressed next.

[23] The Secretary cites in part, transcript pages 73-76 and 95. It is not clear how these citations advance the Secretary's argument.

VII. Potential Alternative Causes

Here, the record includes suggestions that two substances, unrelated to the HPV vaccination, could have caused Ms. Stricker's illness. These are her use of tetracyclines and her exposure to the HPV virus.

A. Tetracyclines

Ms. Stricker started using minocycline for her acne in 2010. Tr. 97, 113. She used it until August 2015, when her acne returned. Tr. 31, 97. Her dermatologist switched her medication from minocycline to doxycycline. Tr. 97, Exhibit 11 at 6 (Aug. 11, 2015). Ms. Stricker stopped taking all tetracyclines by mid-November 2015. Tr. 98, 113.

Ms. Stricker's use of minocycline and doxycycline are the foundation for Dr. Rose's idea that Ms. Stricker suffered from drug-induced lupus. See Tr. 529. Drug-induced lupus is not the same as SLE. Tr. 608.

To evaluate whether a tetracycline caused Ms. Stricker's health problems, Dr. Rose's proposal will be analyzed via a structure based upon Althen. See Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 549 (Fed. Cir. 1994) ("the standards that apply to a petitioner's proof of actual causation in fact in off-table cases should be the same as those that apply to the government's proof of alternative actual causation in fact"); Oliver v. Sec'y of Health & Hum. Servs., No. 10-394V, 2017 WL 747846, at *24-27 (Fed. Cl. Spec. Mstr. Feb. 1, 2017) (following this method of analysis), mot. for rev. denied, 133 Fed. Cl. 341 (2017), aff'd, 900 F.3d 1357 (Fed. Cir. 2018).

1. Prong One – Can Cause

The evidence supports a finding that tetracyclines can cause drug-induced lupus. Two potentially overlapping reasons support this finding. First, examples of minocycline use preceding the development of lupus symptoms appear in two articles, El-Hallak and Lawson. While these two articles could be aptly described as case series in that they present sequences of events (and, therefore, carry relatively little value on causation), the Lawson article is different. Some of the subjects in Lawson used minocycline, developed problems, stopped the drug with improvement in problems, restarted the drug, and again experienced health problems. Lawson at 330, Tr. 609. These are examples of challenge-rechallenge, which is strong proof of causation. Capizzano, 440 F.3d at 1322; R.S. v. Sec'y of Health & Hum. Servs., No. 15-1207V, 2021 WL 6502227, at *14 (Fed. Cl. Spec. Mstr. Dec. 15, 2021).

Second, and perhaps relatedly, Dr. Zizic did not challenge the proposition that tetracyclines can cause drug-induced lupus. See Tr. 177, 284, 349-50. Similarly, Ms. Stricker did not argue that tetracyclines cannot cause drug-induced lupus. See Pet'r's Posthear'g Br. at 69. Thus, there is sufficient evidence to conclude that tetracyclines can cause drug-induced lupus. See Watts v. Medicis Pharma. Corp., 365 P.3d 944, 947 ¶ 3 (Ariz. 2016).

2. Prong Three – Timing

The third Althen prong requires "a showing of a proximate temporal relationship between vaccination and injury." This point is based upon each vaccination being a discrete one-time to event. However, Ms. Stricker ingested tetracyclines for approximately four years. Tr. 529, 607, 611. According to Dr. Rose, Ms. Stricker's greater exposure to minocycline made it more likely for her to develop an adverse reaction. Tr. 612.

The El-Hallak article presents a series of 27 people with chronic minocycline-induced lupus. The mean duration of minocycline use before the onset of symptoms was 13.0 months ± 10.8 months. El-Hallak at 315, Tr. 534. Thus, the onset of Ms. Stricker's lupus symptoms is within a medically appropriate time. Again, neither Dr. Zizic nor Ms. Stricker raised any persuasive objection regarding the *onset* of the lupus problems vis-à-vis her use of minocycline.

3. Prong Two – Logical Sequence

The second Althen prong concerns "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Here, Ms. Stricker contends that she did not (and does not) have minocycline-induced lupus for various reasons. The first point is that the removal of the drug usually causes symptoms to improve. Contrary to this general principle, after Ms. Stricker stopped taking doxycycline in mid-November, she declined over Thanksgiving and into Christmas. Tr. 228-29 (Dr. Zizic), 529 (Dr. Rose), 608 (Dr. Rose on cross-examination), 614 (same). This reasoning was adopted by a dermatologist who treated Ms. Stricker. Relying upon Lawson, Dr. Breza wrote: "Given that the patient[']s symptoms have not resolved several years after discontinuation of minocycline, I can be certain that minocycline was not the cause of her connective tissue disorder." Exhibit 24.

However, the El-Hallak article presents examples of people with lupus problems that persisted after they stopped taking minocycline. Tr. 534. Indeed, the title is "Chronic Minocycline-Induced Autoimmunity in Children." El-Hallak

at 314. In other words, the patients' lupus "did not go away." Tr. 534. These reports counter and undermine the opinion of Dr. Breza.

Ms. Stricker's series of health problems in November and December 2015 reminded Dr. Rose of a case of minocycline-induced lupus in a patient he treated. Tr. 531. Similar features included an acute onset of problems, a vasculitic rash, constitutional symptoms, low ANA, robust sed rate, and minor to moderate liver abnormalities. Id. To Dr. Rose, Ms. Stricker "really looked like a [minocycline-induced lupus] patient." Tr. 532. Dr. Zizic did not rebut this opinion from Dr. Rose.

The key question from Dr. Rose's perspective is whether Ms. Stricker's symptoms have resolved in the intervening years. Tr. 533. Dr. Rose identified the following diagnostic possibilities for Ms. Stricker:

(1) She had minocycline-induced lupus and still has symptoms of minocycline-induced lupus
(2) She had minocycline-induced lupus and now has symptoms of systemic lupus erythematosus,
(3) She had minocycline-induced lupus and has stopped having symptoms of minocycline-induced lupus, or
(4) She never had minocycline-induced lupus.

A person with minocycline-induced lupus can develop "real" lupus. Tr. 630. For example, a patient in El-Hallak's collection developed antibodies to double-stranded DNA. El-Hallak at 316, Tr. 760.

A continuation of symptoms can occur too. For example, the El-Hallak group followed patients with chronic minocycline-induced lupus for as many as 48 months. El-Hallak at 317 (Table 3), Tr. 535-36, 749-50. One patient still had symptoms after 48 months.

Whether Ms. Stricker's lupus symptoms persist is far from clear. She has been taking Plaquenil. Her rheumatologist, Dr. Saba, has not noted any joint involvement Tr. 616, see also Resp't's Posthear'g Br. at 23-24 (citing medical records). But, a potentially confounding factor is that Ms. Stricker testified she no longer complains to Dr. Saba about her joint problems. Tr. 128-31.[24]

[24] A lack of complaint would not necessarily preclude Dr. Saba from observing joint swelling. See Tr. 411-12 (Dr. Rose's description of how rheumatologists examine patients).

4. Summary

If Ms. Stricker had presented persuasive proof on all three Althen prongs and thereby shifted the burden of proof to the Secretary, the Secretary could not succeed in showing on a more likely than not basis that tetracycline induced Ms. Stricker's lupus. Dr. Rose conceded that SLE is an appropriate diagnosis for Ms. Stricker and minocycline-induced lupus is a less likely alternative. Tr. 529-30.

But, on the other hand, to the extent that the presence of potential alternative causes can be considered as part of the second prong of Althen, the evidence regarding tetracycline weakens Ms. Stricker's case. See Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012); Doe 11 v. Sec'y of Health & Hum. Servs., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010). Among these two alternatives (HPV vaccine and tetracyclines), tetracycline is a better explanation.[25] As discussed above, the evidence shows minocycline can cause a drug-induced lupus at least rarely. In contrast, the evidence does not preponderate in favor of finding that the HPV vaccination can cause SLE. This disparity means that tetracycline is a more likely explanation even if the likelihood of tetracycline is not more likely than not. See Caves, 100 Fed. Cl. 119, 143 n.17 (explaining that the "most likely" cause is not always "more likely than not").

B. HPV Infection

In addition to tetracycline, the Secretary suggests Ms. Stricker's HPV infection could have caused her lupus. The structure for the analysis also follows the Althen prongs.

1. Prong One – Can Cause

The parties did not dispute HPV infection can cause SLE. Citing Shi, Dr. Moy proposed this alternative cause in his first report. Exhibit A at 6. Dr. Moy repeated this opinion in his oral testimony. Tr. 678-79. Dr. Zizic also testified that the HPV infection can cause SLE. Tr. 169, 324. Based upon this agreement, further discussion is not needed.

[25] Ms. Stricker's health problems may not have been caused by either the HPV vaccine or tetracyclines because the cause of SLE in the vast majority of cases is unknown. See Gulati & Brunner at 710; see also Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1354 (Fed. Cir. 2008) ("a failure of proof that the vaccine was the cause of the petitioner's injury suggests that some other cause was responsible").

2. Prong Three – Timing

Here, the medically acceptable latency between an HPV infection and the development of lupus was unclear and complicated. The Shi article does not present any information about how long people with an HPV infection were infected before manifesting symptoms or signs of lupus. See Shi; see also Tr. 680.

One of the problems with determining a medically acceptable latency is that the date of infection is rarely, if ever, known. For example, although Ms. Stricker's HPV infection was discovered via a Pap smear on August 11, 2015, she was not symptomatic. Exhibit 7 at 83, Tr. 213, 242, 604, 680.

Another complication is how the HPV virus acts after transmission. An HPV virus can be dormant. Tr. 681, 684. During this time, the HPV virus hides from the immune system. Tr. 588, 684, 688; see also Godfrey v. Sec'y of Health & Hum. Servs., No. 10-565V, 2014 WL 3058353, at *9 (Fed. Cl. June 11, 2014), mot. for rev. granted in non-relevant part, 2015 WL 4972882 (Fed. Cl. 2015). Then after a period of being dormant, the virus can activate and begin replicating. Tr. 604-06, 684. How any activation and replication might cause SLE was not explained well. Cf. Tr. 686 (suggesting molecular mimicry might be a mechanism). Dr. Moy suggested a person could be infected with HPV virus for two years before developing SLE. Tr. 681, 684. The basis for this opinion was not explained persuasively.

The lack of reliable evidence about a medically acceptable interval between HPV infection and onset of lupus is an obstacle to finding that Ms. Stricker's lupus developed within an appropriate time of her HPV infection. Before she began to display symptoms of lupus around November 1, 2015, she most recently had engaged in sexual activity in August 2014. Tr. 88. The transmission of a sexually communicated virus could have occurred even earlier. Tr. 243. Thus, the latency must have been at least one year. See Tr. 604. Dr. Zizic was skeptical that a latency of more than one year was appropriate. He described this idea as "highly improbable." Tr. 243. Accordingly, a preponderance of the evidence does not support a finding that Ms. Stricker's lupus symptoms developed within the medically appropriate time after she contracted the HPV virus.

3. Prong Two – Logical Sequence

To complete the topic of the HPV infection as a cause for Ms. Stricker's lupus, the second Althen prong is briefly reviewed. Again, the reports from treating doctors are entitled to consideration. Here, no treating doctor associated

Ms. Stricker's lupus with her HPV infection. Tr. 696. This lack of attribution tends to diminish the value of the theory that an HPV infection caused Ms. Stricker's lupus.

4. Summary

Due to the resolution of other issues, resolving whether the HPV virus caused Ms. Stricker's lupus is not required. However, to the extent a conclusion is needed, the evidence that the HPV virus caused Ms. Stricker's lupus is slightly stronger than the evidence that the HPV vaccine caused Ms. Stricker's lupus. Much like the analysis of tetracyclines, the analysis of HPV infection favors a finding that the HPV infection can cause SLE. This finding makes an infectious cause more likely than a vaccine cause. However, the infectious cause itself remains very unlikely due to the uncertainties for timing.

VIII. Conclusion

The onset of lupus symptoms within approximately six weeks of the HPV vaccination understandably raised a suspicion in the minds of Ms. Stricker and her mother that the HPV vaccine caused Ms. Stricker's SLE. However, the evidence, considered as a whole, does not preponderate in favor of in finding that Ms. Stricker met her burden of proof. The primary deficiency is that she has failed to present a persuasive theory explaining how an HPV vaccine can cause SLE. In addition, her use of tetracyclines provides a viable alternative explanation of her symptoms.

The Clerk's Office is instructed to enter judgment in accord 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, which are available on the website for the Court of Federal Claims.

IT IS SO ORDERED.

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

Appendix containing list of Works Cited[1]

1. M. Abu-Shakra et al., Influenza Virus Vaccination of Patients with SLE: Effects on Generation of Autoantibodies, 21 CLIN. RHEUMATOL. 361 (2002); filed as Exhibit 52.

2. Lisen Arnheim-Dahlström et al., Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study, 347 BMJ 15906 (2013); filed as Exhibit R.

3. Hilda Bastian, What the systematic review of HPV vaccine clinical study reports does, and does not, reveal: commentary on Jørgensen et al., 9 SYST. REV. 41 (2020); filed as Court Exhibit 1001.

4. C. Chao et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine, 271 J. INTERN. MED. 193 (2012); filed as Exhibit Q.

5. J. Patricia Dhar et al., The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus, 9 VACCINE 2642 (2017); filed as Exhibit W.

6. A. Doria et al., Infections as triggers and complications of systemic lupus erythematosus, 8 AUTOIMMUN. REV. 24 (2008); filed as Exhibit 49.

7. Moussa El-Hallak et al., Chronic minocycline-induced autoimmunity in children, 153 J. PEDIATR. 314 (2008); filed as Exhibit M.

8. Mariele Gatto et al., Human papillomavirus vaccine and systemic lupus erythematosus, 32 CLIN. RHEUMATOL. 1301 (2013); filed as Exhibit 63.

9. David A. Geier & Mark R. Geier, A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events, 35 CLIN. RHEUMATOL. 1225 (2015); filed as Exhibit 64 and Exhibit 95.

[1] Although all articles have been considered, this appendix provides bibliographic information for articles cited in the decision.

10. Lamiae Grimaldi-Bensouda et al., Risk of autoimmune diseases and human papillomavirus (HPV) vaccines: Six years of case-referent surveillance, 79 J. AUTOIMMUN. 84 (2017); filed as Exhibit V.

11. Guarav Gulati & Hermine I. Brunner, Environmental triggers in systemic lupus erythematosus, 47 SEMIN. ARTHRITIS RHEUM. 710 (2018); filed as Exhibit J.

12. Lars Jorgensen et al., Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports, 9 SYST. REV. 43 (2020); filed as Exhibit 82.

13. Darja Kanduc, Peptide cross-reactivity: the original sin of vaccines, 4 FRONT. BIOSCI. 1393 (2012); filed as Exhibit 54.

14. T. M. Lawson et al., Minocycline-induced lupus: clinical features and response to rechallenge, 40 RHEUM. (OXFORD) 329 (2001); filed as Exhibit N.

15. Erin Y. Liu, Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study, 190 CMAJ E648 (2018); filed as Exhibit T.

16. Sara Miranda et al., Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France, 35 VACCINE 4761 (2017); filed as Exhibit S.

17. Christine G. Parks, Understanding the role of environmental factors in the development of systemic lupus erythematosus, 31 BEST PRACT. RES. CLIN. REHUMATOL. 306 (2017); filed as Exhibit H.

18. Noel R. Rose, Infection and autoimmunity: theme and variations, 24 CURR. OPIN. RHEUMATOL. 380 (2012); filed as Exhibit 39.

19. L. H. Shi et al., Risk of systemic lupus erythematosus in patients with human papillomavirus infection: a population-based retrospective cohort study, 27 LUPUS 2279 (2018); filed as Exhibit K.

20. Yahel Segal et al., HPV and systemic lupus erythematosus: a mosaic of potential crossreactions, 65 IMMUNOL. RES. 564 (2017); filed as Exhibit 60.

21. F. H. Soldevilla, Systemic lupus erythematosus following HPV immunization or infection?, 21 LUPUS 158 (2012); filed as Exhibit 62.

22. N. Toplak & T. Avclin, Vaccination of healthy subjects and autoantibodies: from mice through dogs to humans, 18 LUPUS 1186 (2009); filed as Exhibit 65.

23. Bin Wang et al., Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis, 16 AUTOIMMUN. REV. 756 (2017); filed as Exhibit 94.