In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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EMILY TARSELL, as the Executrix of the Estate of CHRISTINA TARSELL, Petitioner,	*	No. 10-251V Special Master Christian J. Moran
	*	Filed: February 16, 2016
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Entitlement; human papillomavirus ("HPV") vaccine; sudden death
* *		

Mark T. Sadaka, Mark T. Sadaka, LLC, Englewood, NJ, for petitioner;
Ann D. Martin, United States Dep't of Justice, Washington, D.C., for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Emily Tarsell alleges that the human papillomavirus ("HPV") vaccine caused her daughter, Christina, to die unexpectedly. Ms. Tarsell, acting as the executrix of Christina's estate, is seeking compensation pursuant to the National Childhood Vaccine Injury Compensation Program, codified at 42 U.S.C. § 300aa−10 through 34 (2012).

After Christina received the first dose of the HPV vaccine, she was diagnosed with a heart problem, known as arrhythmia. The arrhythmia is likely to have caused Christina's death.

[1] The E-Government, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

To connect the HPV vaccination and Christina's arrhythmia, Ms. Tarsell relies upon the opinion of an immunologist, Yehuda Shoenfeld, and a cardiologist, Michael Eldar.[2] Dr. Shoenfeld asserted that the arrhythmia developed after the first HPV vaccination. Dr. Shoenfeld and Dr. Eldar opined that the HPV vaccine caused the arrhythmia, which led to Christina's death.

The Secretary disagreed with Ms. Tarsell's claim. The Secretary presented the opinions of cardiologist Scott Yeager and immunologist S. Michael Phillips.[3] Dr. Yeager opined that the onset of Christina's arrhythmia is unknown. Dr. Yeager and Dr. Phillips opined that evidence did not support the causal mechanism proposed by Ms. Tarsell's two experts.

Ms. Tarsell has not met her burden of establishing her case with preponderant evidence. Ms. Tarsell has not persuasively established a basic proposition of her claim, that Christina did not experience an arrhythmia until after the first dose of the HPV vaccine. Without this foundation, the rest of Ms. Tarsell's claim cannot stand. In addition, even if Christina's arrhythmia did arise after the vaccination, the proposed theory contains too many leaps and unsupported assumptions to be persuasive. Furthermore, a study of Christina's heart tissue that pathologists at the Centers for Disease Control and Prevention ("the CDC") conducted showed that Christina did not experience damage in the way her experts' theories predicted. Consequently, despite the sympathetic position of Ms. Tarsell as the mother of a woman who died far too early, Ms. Tarsell is not entitled to compensation.

I. Background

The relevant facts include information from Christina's life as well as the way that she died – suddenly and unexpectedly.

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[2] Dr. Shoenfeld, whose *curriculum vitae* spans over 120 pages, has nearly 40 years of researching autoimmune response, writing numerous articles on the subject. Exhibit 37. Dr. Shoenfeld has testified previously before the Vaccine Program. Dr. Eldar also has nearly 40 years of experience authoring over 170 articles. Exhibit 137.

[3] Dr. Yeager has written more than 90 peer-reviewed reports, abstracts, book chapters, and presentations in cardiology over his 40-year career. Exhibit GG. Dr. Phillips's 50 years of research experience has produced more than 130 original papers, editorials, reviews, chapters, and books. Exhibit B.

A. Christina's Medical History

In May 2008, Christina had just completed her third year of college, where she was studying art and playing tennis. Athletics had been part of Christina's life for many years. She played tennis even though during one sports physical, a doctor detected an irregular pulse.

After Christina's end-of-the-semester college exams in 2008, and before starting a job at a museum, Christina visited her parents in Maryland. While visiting her parents, Christina received the third dose of the HPV vaccine on June 3, 2008. Exhibit 3 at 99. On June 5, 2008, 2 to 12 dots appeared on Christine's neck near her right ear. Exhibit 15 ¶ 4. On June 7, 2008, Christina felt dizzy and faint. Findings of Fact, issued Mar. 30, 2012, at 7.

Christina returned to her college apartment on June 12, 2008. In the following week, Christina worked at an art museum four days, including Thursday, June 19, 2008. Exhibit 22 at 277. Later that day, Christina ate dinner with her apartment mates. They talked until the early morning on Friday, June 20, 2008. Exhibit 6 at 152.

On Monday, June 23, 2008, Christina did not report for work. One of her apartment mates investigated and found Christina in her bed, unresponsive. Exhibit 6 at 152. The undersigned found that Christina had died on Saturday, June 21, 2008 at approximately noon. Findings of Fact at 9.

A medical examiner, Keri Reiber, performed an autopsy on June 24, 2008. Dr. Reiber found that the cause of Christina's death was cardiac arrest of an undetermined cause. Exhibit 8 at 158. Knowing that Christina had received the HPV vaccine in the days prior to her death, Dr. Reiber reported the death to VAERS and sent tissue to the CDC for further examination. Id.; exhibit 10.

The CDC's Infectious Disease Pathology Branch performed a microscopic examination of Christina's heart tissue. The results showed that the heart tissue exhibited no "conspicuous inflammatory cell infiltrates." Exhibit 10 at 170.

Christina's mother holds the opinion that the cause of her beloved daughter's death was the HPV vaccine. Ms. Tarsell talked about Christina's life and her death with local media. Exhibit 23, 26. The emotion apparent in those videotapes is consistent with the demeanor Ms. Tarsell presented during her testimony. Tr. 19-24. There is no doubt that Christina was a wonderful young adult, whom Bard College honored with an honorary degree the year after her premature death. Tr.

20. Ms. Tarsell is certainly entitled to sympathy for having endured the loss of her only child at a premature age. But, sympathy is not a basis for awarding compensation in the Vaccine Program. 42 U.S.C. § 300aa–13; Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (noting that special masters are responsible for "the unenviable job of sorting through these painful cases").

Setting aside emotion, what is the basis for concluding that the HPV vaccine caused Christina's death? Some reasons lie in Christina's early medical history.

Christina was born in 1986. Her early medical history contains typical illnesses. Exhibit 1 at 15-40. As mentioned earlier, Christina played sports. Tr. 21. Her participation in sports required her to have physical examinations at which her pulse was measured periodically. The list of measurements is presented in the following chart:

Date	Context	Pulse	Citation
8/14/01	Routine assessment. Age 14, 9 months.	72	Exhibit 1 at 19
7/18/02	Routine assessment. Age 15, 8 months.	60	Exhibit 1 at 18
11/29/02	Pulled muscle	70	Exhibit 1 at 17
2/28/05	Motor vehicle accident	76	Exhibit 1 at 8
6/16/05	Physical for college	104	Exhibit 2 at 78
6/23/06	Routine preventative medicine visit	84	Exhibit 1 at 5
8/22/07	Annual gynecologist visit. First dose of HPV vaccine given.	Not noted but cardiovascular is marked negative	Exhibit 3 at 109
9/12/07	Pre-participation Physical evaluation	72; heart, murmurs, and pulses marked normal	Exhibit 2 at 87-88
11/20/07	Dr. Lafferman. Second dose of HPV vaccine given.	Irregular	Exhibit 4 at 136

Dr. Lafferman's detection of an irregular pulse on November 20, 2007, was the first time a doctor discovered an irregularity in Christina's cardiac rhythm.[4] This discovery occurred approximately three months after Christina received the first dose of the HPV vaccine. Exhibit 3 at 109-10.

This discussion about Christina's irregular heartbeat requires a brief (and simplified) digression about regular heartbeats. The heart pumps blood by contracting. Tr. 42-43; Dorland's Illus. Med. Dictionary, at 825-26 (32d ed. 2012). A normal rate of contraction is typically around 60 beats per minute, but the rate can range from 40 to 200. Tr. 44.

The rate of contraction is controlled by the autonomic nervous system. Tr. 45; Dorland's at 1859. The autonomic nervous system sends electrical current throughout the heart. Tr. 45-49.

These electrical signals initiate a process known as polarization, depolarization, and repolarization. Tr. 52-58; Dorland's at 495 (depolarization), 1484 (polarization), 1625 (repolarization). The polarization-depolarization-repolarization cycle involves the passage of different ions through channels, such as sodium channels. Another type of channel involved in the cycle is a calcium channel. Dorland's at 337; Tr. 54. The polarization-depolarization-repolarization process is depicted in electrocardiograms. Dorland's at 599; Tr. 62.[5]

When the heart functions normally, the heart follows an expected rhythm. When not normal, the person suffers from "arrhythmia." Tr. 61; Dorland's at 133. One type of arrhythmia is known as "bigeminy," which means the second beat is abnormal. Tr. 495-96; Dorland's at 214.

Dr. Lafferman detected an irregular heartbeat on November 20, 2007. She described it as "bigeminy." Exhibit 4 at 136. Dr. Lafferman ordered an electrocardiogram, which was also conducted on November 20, 2007. The EKG was abnormal. The report stated "[p]remature ventricular complexes." Id. at 142. Dr. Lafferman also administered the second dose of the HPV vaccine on November 20, 2007. Exhibit 3 at 124.

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[4] Ms. Tarsell argues that this detection in November 2007 implies that the irregularity developed shortly before November 2007. However, as discussed in section IV below, the Secretary disagrees with this reasoning.

[5] "Electrocardiogram" is abbreviated both ECG and EKG. Tr. 59; Dorland's at 599.

Approximately one month later, on December 27, 2007, Christina had a follow-up appointment. Her heartbeat was again irregular. Exhibit 4 at 135. An EKG showed the same pattern as the November 20, 2007 EKG. Exhibit 4 at 141; Tr. 83 (Dr. Eldar), 504 (Dr. Yeager).[6] Dr. Lafferman recommended an echocardiogram.

Christina had an echocardiogram on February 12, 2008. The heart structure was found to be normal. Exhibit 4 at 139; see also Tr. 146 (Dr. Eldar), 510-11 (Dr. Yeager). In Dr. Yeager's opinion, Christina did not have an irregular heart rhythm when the echocardiogram was performed. Tr. 511-12. Christina's doctors did not recommend a Holter monitor or periodic follow-up. Consequently, Christina's next medical appointment was on June 3, 2008, when, as noted above, she received the third dose of the HPV vaccine.

Christina's death on June 21, 2008, was both sudden and unexpected. After an autopsy, the medical examiner, Dr. Reiber, determined that both the cause of Christina's death and the manner of her death were "undetermined." Exhibit 8 at 158.

In this litigation, Ms. Tarsell's experts offer a cause for Christina's death: the HPV vaccinations. However, before discussing the theory by which the vaccination could have led to Christina's death, it is worthwhile to place Christina's death in the context of other sudden unexplained deaths.

B. Sudden Unexplained Deaths

The unrebutted evidence is that in 2008, Christina was not the only American woman who received the HPV vaccine and then died suddenly and unexpectedly. Statistical information suggests that approximately 159 other young women also unexpectedly died after receiving the HPV vaccine. The source of this estimate was Dr. Phillips. Tr. 342-48; see also Tr. 518 (Dr. Yeager). Dr. Phillips was qualified to explain epidemiological studies. Tr. 335-38.

Ultimately, Dr. Phillips's opinion was that the HPV vaccination did not cause Christina's death. Tr. 338-39. In the absence of a causal relationship, a

[6] The report from the December 27, 2007 EKG stated Christina had "atrial fibrillation." The finding that Christina's premature contractions came from her atria was mistaken. The testifying cardiologists agreed that the contractions actually originated from Christina's ventricles. Tr. 67-68 (Dr. Eldar), 502 (Dr. Yeager).

connection between the vaccination and Christina's death is coincidental. See Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317 (Fed. Cir. 2006); Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144 (Fed. Cir. 1992).

Several epidemiological studies did not find an increased rate of sudden and unexplained deaths after HPV vaccination. Two epidemiological studies that looked for numerous adverse effects of an HPV vaccine were exhibit 109 (Chun Chao et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine, 271 J. Intern. Med. 193 (2012)) and exhibit 95 (Barbara A. Slade et al., Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine, 302 JAMA 750 (2009)). The Chao study evaluated medical records of over 189,000 women after receipt of each dose of the HPV vaccine for new onset of autoimmune conditions. The researchers compared their health to that of the control group of unvaccinated women. The study found no evidence linking the HPV vaccine to autoimmune conditions. Exhibit 109 at 1. The Slade group of researchers investigated HPV VAERS reports from June 1, 2006 to December 31, 2008. There were 32 reported deaths following vaccination with six being cardiac-related. The researchers performed a clinical review of medical records and autopsy reports determining that the deaths reported were attributable to causes other than the vaccine. Exhibit 95 at 6. Other studies focused on any evidence of an increased rate of death following HPV vaccine.

In Dr. Phillips's estimation, the strongest study was reported by the Australian government. Tr. 471. In Australia, nearly seven million doses of the HPV vaccine were distributed between 2007 and 2013. There were no reports of "deaths directly linked to the vaccine." Exhibit PP (Austl. Gov't Dep't of Health Therapeutic Goods Admin., Gardasil (quadrivalent human papillomavirus vaccine), update 1 (Apr. 25, 2014), http://www.tga.gov.au/safety/alerts-medicine-gardasil-130516.htm.) at 2.

Ms. Tarsell's experts did not challenge the Australian report, leaving Dr. Phillips's testimony unrebutted. One of Ms. Tarsell's experts, Dr. Shoenfeld, dismissed the findings from Chao because of a potential conflict of interest. Tr. 213. Dr. Shoenfeld appeared to approve the work by Slade as Dr. Shoenfeld cited that study in connection with his opinion on the appropriate temporal relationship. Tr. 255-58.

In addition to criticizing some (but not all) of the epidemiological studies upon which the Secretary relied, Dr. Shoenfeld also attempted to draw support

from a study authored by Eva Vanamee and colleagues. When the authors submitted the manuscript for publication, two peer reviewers rejected it. Tr. 250.

In their work, Vanamee and colleagues re-analyzed data that the manufacturer of the HPV vaccine, Merck & Co., Inc., presented to the Food and Drug Administration. They found that in the first month after vaccination, four vaccinees died. See exhibit 38 (Eva Vanamee et al., An independent review of the Gardasil clinical trial data: Do the benefits outweigh the risks (unpublished manuscript) (on file with the clerk's office)) at 4-6. From this piece of datum, Vanamee concluded that the HPV vaccine may be contributing to an increased risk of deaths.

Dr. Phillips opined that the Vanamee study was not reliable. Tr. 352. Vanamee appeared to ignore additional details about the context of the deaths. For example, one death was attributed to a trauma that followed a car accident. See exhibit 81 (Memorandum from Nancy B. Miller, Medical Officer, Food and Drug Administration (June 8, 2006) (on file with the clerk's office)) at 190. Dr. Shoenfeld's opinion was that the vaccination was still the reason for the death either because the reporter of information manipulated the data or because the vaccination impaired the person's ability to operate a car. Tr. 262-65. Dr. Shoenfeld's opinion on this point is not credible as he had no foundation for his charges.[7] Instead, Dr. Phillips's opinion that the Vanamee study was not reliable is more persuasive.[8]

Without the Vanamee study, all the epidemiological evidence points in one direction. As Dr. Phillips explained, some epidemiological studies are designed well and others are not designed well. The particular strengths and weaknesses of any particular epidemiologic study are relatively unimportant because the findings

[7] Dr. Shoenfeld appears to be developing a propensity for selective ad hominem attacks. When researchers such as Dr. Chao find no evidence that a vaccine is causing an increased incidence of disease, Dr. Shoenfeld attacks the integrity of the researcher. However, Dr. Shoenfeld readily accepts the reports of a vaccination preceding the onset of various diseases without considering the bias or prejudice of those reporters.

[8] After the hearing, Ms. Tarsell did not cite the Vanamee study in her brief. The Secretary argued that Ms. Tarsell "has abandoned any reliance on it." Resp't's Posth'g Br. at 17. In her reply brief, Ms. Tarsell did not respond to this contention and also did not cite the Vanamee paper.

that HPV vaccination has not caused an increase in the rate of death in the relevant population are consistent across many studies. Tr. 349-51.

The Secretary "is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief." Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008). In a case from the beginning of the Vaccine Program, the Federal Circuit stated "epidemiological studies are probative medical evidence relevant to causation." Grant, 956 F.2d at 1149 (Fed. Cir. 1992). On the other hand, a special master may not deny compensation simply because a petitioner has failed to introduce epidemiologic studies. Capizzano, 440 F.3d at 1325 (Fed. Cir. 2006).

The Secretary's epidemiologic evidence in this case is comparable to the approach the Secretary took in the Omnibus Autism Proceeding. There, the special masters considered a multitude of epidemiologic studies that investigated whether various vaccinations caused autism and found no causal relationship. The special masters found that the epidemiologic evidence was one reason --- but not the only reason --- for finding that the petitioners failed to carry their burden in those cases. See, e.g., Cedillo v. Sec'y of Health & Human Servs., No. 98-916V, 2009 WL 331968, at *84-93 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 89 Fed. Cl. 158 (2009), aff'd, 617 F.3d 1328 (Fed. Cir. 2010); Hazlehurst v. Sec'y of Health & Human Servs., No. 03-654V, 2009 WL 332306, at *34-39 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 88 Fed. Cl. 473 (2009), aff'd, 604 F.3d 1343 (2010).

However, after resolution of the test cases in the Omnibus Autism Proceeding, the Federal Circuit issued Koehn v. Sec'y of Health & Human Servs., 773 F.3d 1239 (Fed. Cir. 2014). In the underlying case, a special master denied compensation, in part, because the epidemiologic evidence was against the petitioner's claim. Koehn v. Sec'y of Health & Human Servs., No. 11-355V, 2013 WL 3214877, at *25-26 (Fed. Cl. Spec. Mstr. May 30, 2013), mot. for rev. denied, 113 Fed. Cl. 757 (2013), aff'd, 773 F.3d 1239 (Fed. Cir. 2013). At the Federal Circuit, two members of the panel stated that the special master erred in evaluating the evidence relating to the first prong of Althen. Although the Federal Circuit did not specify the actual errors the special master made, the broad language in Koehn at least raises a question about relying upon epidemiologic evidence. 773 F.3d at 1244 n.1. But, this interpretation of Koehn might itself be problematic because several other Federal Circuit cases have endorsed a special master's reliance on epidemiologic studies. See Hunt v. Sec'y of Health & Human Servs., No. 12-232V, 2015 WL 1263356, at *17 n.18 (Fed. Cl. Spec. Mstr. Feb. 23, 2015), mot. for rev. denied, 123 Fed. Cl. 509 (2015); Holt v. Sec'y of Health & Human

Servs., No. 05-136V, 2015 WL 4381588 at *30 n.84 (Fed. Cl. Spec. Mstr. June 24, 2015), mot. for review filed (July 23, 2015).

Regardless of any questions about how special masters may rely upon epidemiological studies, it is clear that some young women die suddenly, unexpectedly, and without any known cause. These deaths shock the affected family and broader community. The deaths of apparently healthy and thriving young people for no reason are "not the way life is supposed to be." Tr. 518 (Dr. Yeager). Yet, they happen regardless of whether the women received any vaccination. Tr. 137 (Dr. Eldar). When researchers have looked to see whether these senseless deaths occur more frequently after the decedent received the HPV vaccination, they have not detected any increase. Thus, the epidemiological studies teach either that the HPV vaccine has not increased the rate of death or if the HPV vaccine is increasing the rate of death, then the increase happens so rarely that multiple studies have not found it.

II. Overview of Ms. Tarsell's Arguments and the Secretary's Responses

Ms. Tarsell claims that Christina's case is not one of these tragic events that statistics would unemotionally predict. She claims Christina's case is an example of the very rare case that statistics cannot detect.

Ms. Tarsell presents opinions from two experts. Dr. Shoenfeld, but not Dr. Eldar, asserts that Christina's arrhythmia began after the first dose of the HPV vaccine. From this assumption, Dr. Shoenfeld then opines that the HPV vaccine caused Christina to develop arrhythmia.

Dr. Shoenfeld begins the explanation for how HPV vaccine can cause a sudden death. His primary theory is that the HPV vaccine causes the body to produce antibodies that are misdirected against a part of the heart, known as an L1 calcium channel. Dr. Eldar finishes Ms. Tarsell's theory. The cumulative damage to the L1 calcium channel impairs the heart's functioning leading to arrhythmia, and arrhythmia caused Christina's death.

The Secretary also presented the opinions of two experts. Dr. Phillips, as just discussed, presented information about epidemiology. He also responded to the immunologic aspects of Dr. Shoenfeld's theory. Dr. Yeager is a cardiologist. Like Dr. Eldar, he did not know when Christina's arrhythmia began.

These experts presented their opinions in a series of reports. Exhibits 36, 94, 101, 108, 138 (all Dr. Shoenfeld); 100, 107, 140 (all Dr. Eldar); A, UU, XX (all

Dr. Phillips); FF, VV, ZZ, OOO (all Dr. Yeager).[9] They and Ms. Tarsell testified at a hearing. Following the hearing, the parties submitted briefs, making the case ripe for adjudication.

III. Standard for Adjudication

A petitioner is required to establish her 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 & Human 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 & Human 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 & Human 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 & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human 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).

The elements of Ms. Tarsell's case are set forth in the often cited passage from the Federal Circuit's decision in Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

IV. Analysis

The three prongs of the Althen test are evaluated in separate sections below. The order of presentation begins with timing because a gap in Ms. Tarsell's evidence is most readily apparent in the context of attempting to identify when

[9] Relatively early in the case, Ms. Tarsell filed a report from Dr. Werner Spitz. Exhibit 32. However, his opinions do not advance Ms. Tarsell's case.

Christina started to suffer arrhythmia. The next issue is the theory or theories that Ms. Tarsell and her experts presented. The last factor is the "logical sequence of cause and effect." Each section analyzes the evidence (medical records, testimony and medical literature) in relation to the relevant precedent.

A. Timing

Ms. Tarsell's first challenge is establishing when Christina's arrhythmia began. When a petitioner cannot establish the onset of the injury the vaccine allegedly caused, the petitioner cannot fulfill the third Althen prong. See Hopkins v. Sec'y of Health & Human Servs., 84 Fed. Cl. 517, 524-27 (2008) (denying motion for review).

Here, the most persuasive evidence indicates that the onset of Christina's arrhythmia is unknown. The arrhythmia could have begun either before or after the vaccination. When Dr. Eldar, Ms. Tarsell's cardiologist, was asked when Christina's arrhythmia began, he stated "I cannot say exactly when it started." Tr. 120. Similarly, when Dr. Yeager, the respondent's cardiologist, was asked when Christina's arrhythmia began, he stated "I don't think I can date when she began having cardiac arrhythmia." Tr. 493. Given their expertise in treating heart problems, Dr. Eldar and Dr. Yeager are credible when their answer essentially is "I don't know when the arrhythmia began."

Ms. Tarsell has no effective response. A close reading of her post-hearing brief reveals that Ms. Tarsell has not proposed any specific date of onset. See Pet'r's Posth'g Br., filed Feb. 17, 2015, at 15-18. Here, Ms. Tarsell states "Christina was a healthy young woman prior to her first [HPV] vaccine. She developed new-onset arrhythmia which did not resolve." The order of these two sentences implies that the vaccination preceded the onset of her arrhythmia.

In making this argument, Ms. Tarsell appears to be following the reasoning of her immunologist, Dr. Shoenfeld. When Dr. Shoenfeld was asked when Christina's cardiac symptoms started, he answered "November 20, 2007," which was the day her irregular pulse was first detected. Tr. 286. When asked to explain the basis for his opinion, Dr. Shoenfeld noted that before the vaccination, none of Christina's treating doctors had found an irregular pulse. Dr. Shoenfeld reasoned "if you don't have an evidence [of an irregular pulse], and then if you have an evidence that the first time was after the second vaccine, it was after the second vaccine." Tr. 287.

Dr. Shoenfeld's conclusion is based on superficial logic and is, ultimately, not persuasive. Dr. Shoenfeld is correct that Dr. Lafferman detected an irregular pulse in Christina for the first time on November 20, 2007. In other appointments, Christina's pulse was measured but no irregularity was detected. For a detailed list of when those appointments occurred, see the table in section I, above. Dr. Shoenfeld assumes that if Christina were suffering from an irregular pulse on the days she was examined, the doctors would have detected it.

Contrary to Dr. Shoenfeld's assumption, people who suffer from arrhythmia do not suffer the arrhythmia continuously. Dr. Yeager explained that a person can have 20 minutes of bigeminy and then a few hours of normal rhythm. Tr. 540. In one study, patients with severe symptomatic arrhythmia wore Holter monitors and, in these patients, abnormal beats were found approximately 17 percent of the time. Exhibit 106 (Takashi Noda et al., Malignant Entity of Idiopathic Ventricular Fibrillation and Polymorphic Ventricular Tachycardia Initiated by Premature Extrasystoles Originating from the Right Ventricular Outflow Tract, 46(7) J. Amer. Coll. Cardiology 1288 (2005)); Tr. 496-97. When the Noda article was brought to Dr. Eldar's attention, he did not dispute Dr. Yeager's opinion. See Tr. 564-65.

Because people with arrhythmia have periods in which their heart beats in normal rhythm, it is not possible to conclude that a doctor's failure to detect an irregular pulse necessarily means that the patient was not suffering from arrhythmia at other times during the day of examination. Tr. 495-96; exhibit OOO (Dr. Yeager Supp'l Rep.) at 3 ("I have no confidence that an unremarkable physical exam tells us anything other than the patient was probably not having a significant arrhythmia during those few seconds of auscultation"). This means that there is no good evidence about when Christina first started to experience the arrhythmia.

The lack of evidence is damaging to Ms. Tarsell's claim for compensation. She bears the burden of establishing when Christina's disease began. See Bazan, 539 F.3d at 1353-54 (Fed. Cir. 2008); Hopkins, 84 Fed. Cl. at 524-27. When there is no persuasive evidence on a particular point, the special master should rule against the party with the burden of proof. See Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 550 (Fed. Cir. 1994) (when the evidence is in equipoise, the party with the burden of proof has failed to carry the burden of persuasion); In re Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder or a Similar Neurodevelopmental Disorder, Master Autism File, 2004 WL 1660351, at *8 (Fed. Cl. Spec. Mstr. July 16, 2004) ("in legal factfinding if there is no evidence, the factual issue simply is resolved against the party having

the 'burden of proof'"). Here, the evidence is not in equipoise. Ms. Tarsell has no persuasive evidence of onset.

While the failure to establish on a more-likely-than-not basis the onset of Christina's arrhythmia is a sufficient basis to resolve Ms. Tarsell's claim that the HPV vaccination caused the arrhythmia that led to Christina's death, this is not the only problem with Ms. Tarsell's case.[10] Accordingly, the other Althen prongs will be analyzed.

B. Theory

If Ms. Tarsell had established that Christina's arrhythmia began after her first HPV vaccination, then, as a matter of logic, the HPV vaccination could have possibly caused the arrhythmia. Cf. Locane v. Sec'y of Health & Human Servs., 685 F.3d 1375, 1381 (Fed. Cir. 2012) (stating that when a disease arises before the vaccination, the "Althen inquiry is inapplicable"). Part of Ms. Tarsell's burden would be to establish, with preponderant evidence, a "causal theory connecting the vaccination to the injury." Althen, 418 F.3d at 1278.

To satisfy her burden under the first prong of Althen, to present a theory causally connecting the HPV vaccine to Christina's death, Ms. Tarsell has advanced the theory of molecular mimicry involving the L1 calcium channels. In addition, she may also be advancing a theory involving beta adrenergic receptors. Because the beta adrenergic theory is more easily addressed, it is considered first.

1. Beta Adrenergic Receptors

Procedurally, whether Ms. Tarsell is proceeding on the beta adrenergic theory is not entirely clear. Dr. Shoenfeld's fourth report disclosed an opinion that a possible defect in Christina's beta adrenergic receptors could have caused her arrhythmia. Exhibit 108 at 9; see also exhibit 36 at 6 (mentioning adrenergic

[10] Conceptually, if the evidence persuasively showed that Christina was suffering from an irregular heartbeat before vaccination, Ms. Tarsell could argue that the vaccination significantly aggravated the pre-existing arrhythmia. Although Ms. Tarsell referenced this theory of recovery in her pre-hearing brief, Pet'r's Preh'g Br. at 17 n.1, 19, Ms. Tarsell did not assert this theory in her posthearing brief or her posthearing reply. If Ms. Tarsell intended to pursue a significant aggravation theory, it was incumbent on her to present evidence that Christina's arrhythmia would not have progressed as it did. See Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 732-33 (2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012).

stimulation but not in the context of Christina's history). However, Ms. Tarsell's pre-trial brief did not reference this theory at all. See Pet'r's Br., filed Sept. 26, 2014, at 13 ("Christina Tarsell died from molecular mimicry and subsequent cross-reactivity between HPV 16 L1 and L-type calcium channel"). Nevertheless, Dr. Eldar and Dr. Shoenfeld discussed beta adrenergic receptors in their testimony and Dr. Yeager responded. Ms. Tarsell included the beta adrenergic theory in her initial brief after the hearing. Pet'r's Posth'g Br. at 12. After the Secretary raised challenges, see Resp't's Posth'g Br., filed Apr. 17, 2015, at 13-14, Ms. Tarsell's reply did not defend the theory at all. Under these circumstances, Ms. Tarsell may have relinquished this theory. But, any potential waiver is academic because Ms. Tarsell has failed to establish the persuasiveness of the beta adrenergic theory.

The beta adrenergic theory focuses on the wiring leading to and existing in the heart. As mentioned earlier, the autonomic nervous system controls the rate at which the heart beats. The autonomic nervous system includes a set of receptors known as beta adrenergic receptors. Dorland's at 33, 1603-04.

One group of researchers investigated whether people suffering from different types of arrhythmias had autoantibodies directed against their beta adrenergic receptors. These researchers found that slightly more than one-half the people with ventricular arrhythmias had anti-beta adrenergic receptor antibodies. The prevalence in the control group was approximately 15 percent. Exhibit 128 (Pablo A. Chiale et al., High Prevalence of Antibodies Against $Beta_1$- and $Beta_2$-Adrenoceptors in Patients With Primary Electrical Cardiac Abnormalities, 26 J. Am. Coll. Cardiol. 864 (1995)) at 864. Dr. Eldar's opinion was that the difference between the two groups "make[s] you think that there is . . . maybe a cause and effect between the one and the other." Tr. 171. From this foundation, Dr. Shoenfeld extended the association to causation, opining that the autoantibodies can cause arrhythmias. Tr. 235; see also Tr. 189 ("pathogenic autoantibodies").

In addition, Dr. Shoenfeld also asserted that the HPV vaccine can induce the creation of antibodies to the beta adrenergic receptors. Tr. 270. For this proposition, Ms. Tarsell's case rests nearly entirely on the simple assertion of Dr. Shoenfeld.

When pressed to explain the basis for his belief that the HPV vaccine can lead to the production of antibodies directed against beta adrenergic receptors, Dr. Shoenfeld relied on a series of articles suggesting that the HPV vaccine caused a different disease, postural orthostatic tachycardia syndrome (POTS). Tr. 279. Dr. Yeager persuasively explained why relying upon a putative connection between

HPV vaccination and POTS cannot serve as a reliable foundation for HPV vaccination and arrhythmia. Tr. 523-27.

Unlike the situation with respect to the L1 calcium channel discussed below, there is no reliable evidence that the HPV vaccine causes the body to produce antibodies to the beta adrenergic receptors in the heart. The only evidence was Dr. Shoenfeld's opinion. Ms. Tarsell has failed to demonstrate that this aspect of his opinion is reliable. See Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 134 (2011) ("it should be obvious to petitioner that a scientific theory that lacks any empirical support will have limited persuasive force"), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012). Dr. Shoenfeld's assertion, by itself, is not persuasive. Doyle v. Sec'y of Health & Human Servs., 92 Fed. Cl. 1, 8 (2010) ("Mere conclusory opinions - or ones that are nearly so as unaccompanied by elaboration of critical premises - will not suffice as proof of causation, no matter how vaunted or sincere the offeror"); see also Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (a special master may find an analytic gap in the opinion of a petitioner's expert that precludes compensation).

Because the beta adrenergic theory does not satisfy Ms. Tarsell's burden on the first Althen prong, her other theory involving the L1 calcium channel will be discussed. The L1 calcium channel is a theory separate from the beta adrenergic theory. See Tr. 150-55 (Dr. Eldar discussing differences between the two theories), 292-93 (Dr. Shoenfeld).

2. Molecular Mimicry with the L1 Calcium Channel

a) Introduction to Molecular Mimicry and Homology

Ms. Tarsell's primary theory is based upon molecular mimicry. Tr. 238. Molecular mimicry posits that the molecular structure of an antigen (like a vaccine) resembles the molecular structure of human tissue. When the body's immune system responds to the antigen, the immune system mistakenly attacks the host. Tr. 193; see also Tr. 375, 418. The term for a similarity in molecular structure is "homology." See Dorland's at 868. Dr. Shoenfeld states that only genetically prone individuals will develop molecular mimicry. Tr. 305.

Dr. Shoenfeld has identified a specific basis for the molecular mimicry between the HPV vaccine and the heart. He relies upon research of computer

databases that identified a particular sequence of amino acids present in both the HPV vaccination and calcium channels found in the heart.[11] Tr. 278-79.

The evidence showing a relevant homology derives from four articles in which Darja Kanduc is either the author or co-author. In the earliest article, Dr. Kanduc stated that her colleagues and she wanted to investigate the belief that "an autoimmune reaction is mostly caused by a host receiving an antigen that has amino acid homology/similarity with amino acid sequences in self-antigens of the host." Exhibit LLL (Darja Kanduc et al., Massive peptide sharing between viral and human proteomes, 29 Peptides 1755 (2008)) at 1755.

Dr. Kanduc used a consistent methodology in the four articles. The foundation for her experiments was that "[p]rotein sequences of the human proteome [12] as well as a number of viral proteomes have become available in databanks." Id. The proteins may contain thousands of amino acids and the relevant calcium channel contains more than 2500 amino acids. Tr. 387, 392 (discussing exhibit FFF (Charles Antzelevitch et al., Loss-of-Function Mutations in the Cardiac Calcium Channel Underlie a New Clinical Entity Characterized by ST-Segment Elevation, Short QT Intervals, and Sudden Cardiac Death, 115 Circulation 442 (2007))). With computers, Dr. Kanduc searched for sequences of amino acids that appear both in the human proteome and in invasive organisms, such as bacteria and viruses. See Tr. 301 (Dr. Shoenfeld), 375 (Dr. Phillips), see also exhibit LLL at 1756-57 (detailed description of methodology). The length of the sequence varied from five amino acids to nine amino acids.[13]

Dr. Kanduc and colleagues tried to identify homologies because "the mathematical quantification of peptide overlap extent between viruses and humans is essential to understand the role of structural viral similarity in the pathogenesis of autoimmunity." Exhibit LLL at 1756. In the earliest experiment reported, the computerized screening found "a massive, indiscriminate, unexpected pentapeptide overlapping between viral and human proteomes." Id. at 1755. Part of the reason

[11] There are 20 amino acids and each amino acid has been assigned a letter. For example, "L" stands for leucine. Dorland's at 60-61, Tr. 377, 389.

[12] A proteome is "the complete set of proteins produced from the information encoded in a genome." Dorland's at 1535.

[13] A sequence of five amino acids is known as a pentamer. See Dorland's at 1407; Tr. 375.

for the overlap is that sequence of amino acids repeat. Mathematically, a sequence of five amino acids contains more than three million combinations. (5^{20} = 3,200,000.) However, less than 10 percent of the pentamers actually appear in either the viral or human proteome. Id. at 1756. The researchers concluded "the mathematical redundancy present in the protein world is not stochastic (i.e. is not pure random chance), but rather reflects strong peptide usage bias since certain peptides are repeatedly used (and shared) in (and among) viral and human proteins." Id. at 1762.

A premise of molecular mimicry is that when invading organisms have a structure similar to the molecular structure of human beings, the body's response to the bacteria or virus can produce an autoimmune reaction. Because Kanduc's 2008 research found "massive" overlap between viruses and humans, "autoimmune diseases should theoretically approach a 100% real incidence." Id. at 1765. However, autoimmune diseases are not that common. Thus, Dr. Kanduc and colleagues stated that their datum "call into question the possibility of a direct causal association between virus-host sharing of amino acid motifs and incitement of autoimmune reactions." Id. at 1755.

In 2009, Dr. Kanduc, writing alone, reported on an experiment using the HPV 16 proteome. She discovered a perfect sequence of seven amino acids 82 times in the human proteome. Exhibit 75 (Darja Kanduc, Quantifying the possible cross-reactivity of an HPV16 vaccine, 8 J. Experimental Therapeutics and Oncology 65 (2009)) at 66. The abstract to the article concluded that "[a]ny antigen-based vaccine needs to be carefully and thoroughly designed and critically screened for potential side effects by comparing sequence similarity at the molecular level." Id. at 65.

Dr. Kanduc, again writing alone, reported about a more specific experiment in 2010. She looked for similarities between a particular portion of the HPV 16 virus known as the L1 capsid and "human proteins that, when altered, are associated with cardiovascular diseases and arrthythmogenic disorders." Exhibit 74 (Darja Kanduc, Potential cross-reactivity between HPV16 L1 protein and sudden death-associated antigens, 9(2) J. Experimental Therapeutics and Oncology, 159 (2010)) at 1. One of these sequences of five amino acids, LQAGL, occurs in the L-type calcium channel. Defects in the L-type calcium channel cause Timothy syndrome and Brugada syndrome. Id. at 5. Dr. Kanduc stated that her finding "suggests that possible immune cross-reactions deriving from utilization of HPV L1 in vaccination might be a source of cardiac implications." Id. at 6.

The final article to which Dr. Kanduc contributed was also published in 2010. A group of researchers, including Dr. Kanduc, compared 40 bacteria with the human genome, looking for matches of nine amino acids. They found more than 47,000 perfect matches, comprising about one-third of the human proteome. Exhibit KKK (Brett Trost et al., Bacterial peptides are intensively present throughout the human proteome, 1 Self/Nonself 71 (2010)) at 71; see also Tr. 376-79 (Dr. Phillips's description of Trost experiment). The authors stated that their findings called into question the molecular mimicry theory. They wrote:

> According to the molecular mimicry hypothesis, the widespread overlap between viral and bacterial proteomes and the human proteome (see Table 1 and ref 5) would predict that autoimmune diseases should have a much higher incidence than actually observed, both in the total number of individuals affected and the number of autoimmune pathologies per individual. Thus, it is difficult to reconcile the enormous number of viral and bacterial peptides disseminated throughout the human proteins with a fundamental role for molecular mimicry in the etiology of certain autoimmune conditions.

Id. at 73.

To some, Dr. Shoenfeld's invocation of molecular mimicry plus an identified homology would constitute a persuasive medical theory.[14] However, the evidence persuasively showed that the LQAGL homology Kanduc discovered in 2009 is not an adequate basis for finding that a cross-reaction actually occurs.

Dr. Phillips explained that it is not entirely unexpected for a particular sequence of amino acids to reappear. Tr. 378-79. Dr. Shoenfeld concurred, stating that there is "a lot of molecular mimicry." Tr. 227. To Dr. Phillips, "showing a homology at a pentameric level — that is, five amino acids — is many steps from showing that that [homology] is causally related to an autoimmune disease." Tr. 375.

[14] Dr. Shoenfeld refrained from describing his theory as "more likely than not." In his view, the theory was "plausible," meaning that it is a "mechanism which is understood [that] can occur." Tr. 268.

b) From Homology to Autoimmune Reaction

Ms. Tarsell did not rest her case simply upon Dr. Kanduc's identification of the LQAGL pentamer in both the HPV16 L1 capsid and the calcium channel. Ms. Tarsell developed a specific application of molecular mimicry by presenting testimony from Dr. Shoenfeld and Dr. Eldar that explains how a homology can lead to a fatal arrhythmia. It appears that the theory contains several discrete assertions. These include the following:

1. The HPV vaccine contains a sequence of amino acids, known as LQAGL. The Secretary agrees with this assertion.
2. The body responds to the HPV vaccine by producing antibodies against the LQAGL sequence.
3. The anti-LQAGL antibodies are produced in large quantities that remain present at meaningful concentrations in the serum.
4. The heart, specifically the L1 calcium channel, contains the LQAGL sequence. The Secretary agrees with this assertion with a caveat, discussed at length below.
5. The antibodies produced in response to the LQAGL sequence in the HPV vaccine cross-react with the LQAGL sequence in the L1 calcium channel of the heart.
6. The damage to the L1 calcium channel in the heart causes arrhythmia.

As noted, the Secretary agrees with two of the six propositions: that the LQAGL sequence appears in the HPV vaccine and this pentamer appears in the L1 calcium channel. This basic homology, as explained above, does not mean that there is a cross-reaction.

For the remaining four assertions, the Secretary has challenged the reliability of the theory. See id. at 11-16. Dr. Phillips stated that Dr. Shoenfeld is not "incorrect," but that he has presented a theory with no evidence. Tr. 380.

c) Response to LQAGL

After an administration of the HPV vaccine, which contains the HPV 16 L1 capsid, the petitioner's theory indicates that the body will respond to the particular sequence of amino acids LQAGL. Dr. Phillips explained why the presence of amino acids L-Q-A-G-L in the HPV vaccine does not necessarily mean that the body actually reacts to that pentamer. He began by explaining that a "protein is a very complex structure. . . [with] primary, secondary, and tertiary structure." Tr. 386. The primary structure refers to a linear sequence, the secondary structure

refers to shapes that the protein can form, and the tertiary structure refers to a three-dimensional configuration. Id. at 386-87. The immune system responds to the antigen in a three-dimensional form. Id. at 387.

Thus, the body must break down the HPV vaccine in exactly the correct way to release the LQAGL peptide. See Tr. 386. Quoting Dr. Phillips's testimony, the Secretary argued that "'there's no guarantee that this short pentamer is going to contribute to that structure.'" Resp't's Posth'g Br. at 10, quoting Tr. 387-88. In reply, Ms. Tarsell did not cite any evidence to refute Dr. Phillips's opinion about how the immune system responds to proteins. See Pet'r's Reply Br., filed May 15, 2015, at 5-6 (stating that Dr. Shoenfeld stated that the LQAGL peptide is contained in the HPV vaccine, but not addressing whether the body would respond to that sequence).

d) Concentration

Assuming that the body produces an immune response to the LQAGL pentamer, the body must produce a sufficient quantity of antibodies that the antibodies can cause damage. Although some Vaccine Program cases have considered issues about dose response curves, see, e.g., Kolakowski v. Sec'y of Health & Human Servs., No. 99-625V, 2010 WL 5672753 at *17-21 (Fed. Cl. Spec. Mstr. Nov. 23, 2010), Snyder v. Sec'y of Health & Human Servs., No. 01-162V, 2009 WL 332044 at *65 (Fed. Cl. Spec. Mstr. Feb. 12, 2004), mot. for rev. denied, 88 Fed. Cl. 706 (2009), the parties did not elicit any testimony about this aspect of petitioner's theory. Because the Secretary did not raise any direct challenge to the amount of antibodies, Ms. Tarsell's lack of evidence is not held against her.

e) Location of the Calcium Channel in Heart

In Dr. Kanduc's 2009 article, she identified the LQAGL pentamer as part of the "[v]oltage-dependent L-type calcium channel subunit alpha-1C." Exhibit 74 at 5. Dr. Kanduc did not provide any additional information about where the protein appears in the heart cells.

The LQAGL pentamer is located on an intra-cellular portion of the calcium channel. See exhibit FFF at 446 (figure D); exhibit 120 (Victor A. McKusick, Calcium Channel, Voltage-Dependent, L-Type, Alpha-1C Subunit; CACNA1C, Online Mendelian Inheritance in Man, OMIM. Johns Hopkins Univ., Baltimore, MD. 114205 (March 19, 2014) http://www.omim.org/); see also Tr. 392-96. Ms.

Tarsell did not dispute this evidence.[15] See exhibit 138 (Dr. Shoenfeld's post-hearing report) at 1.

The Secretary argues that the location of the LQAGL pentamer makes Ms. Tarsell's theory less likely. Usually, antibodies react with material located outside of the cell membrane. See Tr. 397. The extra-cellular location allows antibodies, which circulate through the blood stream, to bind to the cognate antigen. In contrast, the relevant pentamer is located on an intra-cellular portion of the channel – behind the cell membrane. The cell membrane generally prevents antibodies from reaching the calcium channel to cross-react with the LQAGL pentamer. Tr. 7; Resp't's Posth'g Br. at 11-12.

To ameliorate the prejudice associated with the late disclosure of exhibit NNN and the late raising of an argument based on the intracellular location of LQAGL, Ms. Tarsell was allowed to file supplemental reports from Dr. Shoenfeld and Dr. Eldar that addressed whether antibodies can penetrate the cell membrane. Tr. 9, 400-01, 571; order, issued Nov. 21, 2014. Ms. Tarsell filed those reports as exhibits 138 and 140.

f) Penetrating Cell Membrane

After the Secretary asserted that any antibodies produced in response to the HPV vaccine could not react with the LQAGL pentamer in the calcium channels of the heart, the parties elicited testimony from the experts about this issue. In addition, Ms. Tarsell was permitted to submit supplemental reports.

Usually, antibodies bind to the outside of a cell, where the antibodies start their attack against an invading organism. See Tr. 397 (Dr. Phillips: "the vast majority of antibodies bind to conformational determinants on the surface of cells"). But, as discussed above, this typical process is not relevant to petitioner's

[15] At the hearing, the Secretary presented one more article locating the pentamer as behind the cell wall. See Tr. 5, exhibit NNN (The Universal Protein Resource ("UniProt"), UniProtKB - Q13936 (CAC1C_HUMAN) Voltage-dependent L-type calcium channel subunit alpha-1C, http://www.uniprot.org/uniprot/Q13936 (last visited Nov. 13, 2014)). Ms. Tarsell, appropriately, objected to the late disclosure of this evidence. Tr. 7-9, 400-01. Substantively, it is not clear that the UniProt article added anything more to the information contained in exhibit 120 and exhibit FFF, which were in the record before the hearing. Nonetheless, the Secretary is expected to be more diligent about disclosing evidence before the hearing.

experts' opinions here because the calcium channel is inside the cell, protected by the cell's membrane. Tr. 398.

When Dr. Shoenfeld was asked whether antibodies can penetrate a cell's membrane, he asserted that they could. He spontaneously referenced a conference devoted to this topic and offered to produce papers on the topic. Tr. 273-75. Then, after the hearing, he identified specific articles discussing the process of endocytosis. Exhibit 138 (Dr. Shoenfeld's Nov. 25, 2014 report).

In the hearing, Dr. Phillips stated that certain antibodies can penetrate the cell membrane and when there is penetration, the antibodies may damage the cell. Tr. 398; see also Tr. 461. Although Dr. Phillips did not raise this point in this context, Christina's autopsy did not show any damage to the cells in her heart. Exhibit 10 at 170; Tr. 481-82.

When the Secretary responded to the post-hearing supplemental reports from Dr. Shoenfeld and Dr. Eldar, the Secretary presented a report from Dr. Yeager. Dr. Yeager recognized that Dr. Shoenfeld relied upon endocytosis, but argued that Dr. Shoenfeld did "not offer any animal or human model of cardiac disease mediated through this mechanism." Exhibit OOO at 2. It seems telling that the Secretary's response about endocytosis came from a cardiologist, not an immunologist (Dr. Phillips).

The evidence, therefore, demonstrates that antibodies can penetrate a cell's membrane. The Secretary's complaint that Ms. Tarsell's evidence on this point is not robust is misdirected because she raised arguments about the intracellular location of the pentamer at the hearing. Compare Resp't's Preh'g Br., filed Oct. 20, 2014, with Tr. 400 (statement from respondent's counsel that Dr. Phillips's report did not disclose an opinion about intracellular antibodies). A more timely presentation by the Secretary would have allowed both parties to develop evidence on this point more thoroughly.

Dr. Phillips stated: "I'm not making a statement that [molecular mimicry] . . . is totally disproven by the fact that [the calcium channel is] intracellular, but I did want to make the point that since it is intracellular, it makes it more difficult for these antibodies . . . to penetrate." Tr. 401-02. The undersigned finds his analysis on this point persuasive.

g) Type of Disease

Assuming that antibodies produced in response to the LQAGL pentamer of the HPV vaccine reach the calcium channel, the final step is to consider how the

antibodies would affect the functionality of that channel. Because the calcium channel is a tube (Tr. 236), the two obvious possibilities are that damage to the tube either lets too much or too little calcium pass or lets too little calcium pass. Tr. 99 (Dr. Eldar), 532 (Dr. Yeager).

The 2009 Kanduc paper on which Ms. Tarsell relies to establish homology provides some guidance as to what happens when the relevant calcium channel is damaged. Dr. Kanduc associated defects in the gene for the LQAGL pentamer with causing two diseases: Timothy's syndrome and Brugada syndrome. Exhibit 74 (Kanduc) at 5; see also Tr. 389. Brugada's syndrome is very distinctive and Christina's electrocardiogram was not consistent with Brugada's syndrome. Tr. 97-98, 529-30; see also Dorland's at 1823. There was also no testimony that Christina suffered from Timothy's syndrome. See Tr. 299-300; see also Tr. 558-59.

After Dr. Shoenfeld disclosed his reliance on the 2009 Kanduc article, Dr. Yeager discussed the implication of relying upon a genetic defect associated with Brugada's syndrome.

> If we are speculating that a hypothetical antibody is stimulating the phenotypic expression of Brugada-associated sudden death, how are we to explain the lack of the electrocardiographic manifestations of the underlying calcium channel disorder? The only electrocardiographic abnormality identified in Christina was her ventricular ectopy, and Brugada Syndrome is not typically associated with increased baseline ventricular ectopy.

Exhibit AAA at 2.

Thus, before the experts testified orally, there was a problem in Ms. Tarsell's evidence. Her experts were proposing a theory that appeared to lead to either Brugada's syndrome or Timothy's syndrome. Yet, Christina did not suffer from either of those problems. See Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012) (finding that special master was not arbitrary in denying compensation when petitioner's theory involved the vaccine causing dysfunction in the autonomic nervous system and the petitioner did not display any problems in her autonomic nervous system); Ricci v. Sec'y of Health & Human Servs., 101 Fed. Cl. 385 (2011) (finding that special master was not arbitrary in denying compensation when petitioner's theory proposed that a vaccine caused

inflammation in the central nervous system and the vaccinee did not show signs of such an injury).

However, Dr. Eldar testified about how problems in the calcium channel would present. He stated that the flow of calcium has been linked to ventricular tachycardia through catecholamines. Tr. 103-04, 568-69; see also Pet'r's Posth'g Br. at 11. He developed this opinion in his report filed after the hearing. Exhibit 140.

Like the Secretary's introduction of exhibit NNN during the hearing, the initial presentation of an opinion involving catecholamines during the hearing caught the opposing party off guard. See Tr. 570. Although the parties did not flesh out this issue fully, there appears to be a reliable basis for finding that if the calcium channel were damaged, the consequence could be a form of ventricular tachycardia. Thus, on this limited point, Ms. Tarsell's case was persuasive.

h) Summary: Theory

The Federal Circuit has stated that petitioner's burden of proof is "more likely than not," not mere plausibility. Moberly, 592 F.3d 1315, 1322 (Fed. Cir. 2010). Decisions from the Court of Federal Claims have followed Moberly. M.S.B. by Bast v. Sec'y of Health & Human Servs., 117 Fed. Cl. 104, 123 (2014), appeal dismissed, 579 F. App'x 1001 (Fed. Cir. 2014); Taylor v. Sec'y of Health & Human Servs., 108 Fed. Cl. 807, 819 (2013).[16]

Here, Dr. Shoenfeld described his theory as "plausible," meaning that it can occur. Tr. 268. It is true that the Secretary has not presented evidence to show that the molecular mimicry theory is impossible. Yet, the Secretary has raised sufficient challenges to the theory that Ms. Tarsell has not met her burden of proof. These challenges include:

[16] Ms. Tarsell argues that her burden is only to present a "'viable' medical theory." Pet'r's Reply Br., at 5, quoting Contreras v. Sec'y of Health & Human Servs., 121 Fed. Cl. 230, 246 (2015), appeal docketed, No. 2015-5097 (Fed. Cir. June 22, 2015). At the Federal Circuit, the Secretary has argued that the formulation of a petitioner's burden on prong 1 set forth in Contreras is not consistent with Moberly. Brief for Respondent-Appellee at 36, Contreras v. Sec'y of Health & Human Servs., No. 2015-5097 (Fed. Cir. Oct. 2, 2015), 2015 WL 5971936, at *36.

- The likelihood that LQAGL homology could be an inconsequential coincidence in light of the relative commonness of pentamer level homology between invasive organisms and the human proteome,
- The likelihood that a human's immune system would recognize and respond to the five particular amino acids LQAGL when the HPV 16 contains thousands of amino acids,
- The likelihood that any antibodies produced in response to the LQAGL pentamer would cross the cell membrane,
- The likelihood that antibodies to LQAGL would inflict autoimmune damage to the calcium channel that would appear as bigeminy, not Brugada syndrome or Timothy's syndrome as genetic studies would predict.

In finding that Ms. Tarsell has not presented reliable evidence to make her theory persuasive, the undersigned does not intend to suggest that either Dr. Shoenfeld or Dr. Eldar were insincere. To the contrary, all the experts generally appeared to express their honestly held opinions about the theoretical basis for the HPV vaccine to cause a fatal arrhythmia and generally expressed those opinions respectfully. Ms. Tarsell's case falls short of the preponderance of evidence standard due to a lack of support. See Caves, 100 Fed. Cl. at 134.

The experts, themselves, recognized that much of the theory remains untested and unexamined. For example, Dr. Shoenfeld stated that the Kanduc article "didn't finish the whole work." Tr. 269. Dr. Shoenfeld asserted that he could continue Kanduc's work by isolating the calcium channels to see if they react with antibodies. See Tr. 271; see also Tr. 300-02. With respect to his opinion that a defect in the calcium channel would manifest differently from Brugada's syndrome or Timothy's syndrome, Dr. Shoenfeld said "We will not know it. We will have to test it." Tr. 300.

Dr. Phillips testified that "showing a homology at a pentameric level . . . is many steps away from showing that that [similarity] is causally related to an autoimmune disease." Tr. 375. He also stated: "I'm not saying that -- that the theory is incorrect, but I'm saying it's an inadequate explanation, and there's no evidence that it was an explanation in this case." Tr. 380. This assessment is accurate.

In stating that (a) the theory is unpersuasive and (b) additional testing could make the theory more persuasive, the undersigned could be viewed as requiring scientific certainty. The undersigned is aware that Ms. Tarsell does not have to

prove her case to that degree. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1380 (Fed. Cir. 2009), Bunting, 931 F.2d at 873. The undersigned recognizes the difference in proof between the preponderance of evidence standard and a beyond a reasonable doubt standard. See Hodges, 9 F.3d at 962 (the "fact that the opinion of petitioner's doctors was rejected does not mean that the Special Master was demanding scientific certainty; he might simply have been demanding some degree of acceptable scientific support"). Here, Ms. Tarsell's evidence does not meet even the simpler more-likely-than-not standard.

V. Logical Sequence

If Ms. Tarsell had established that the HPV vaccine can, as a theoretical matter, cause arrhythmia and if she had established that Christina's arrhythmia arose in a time interval for which an inference of causation is appropriate, then Ms. Tarsell would also be required to present preponderant evidence that "a logical sequence of cause and effect" linked the HPV vaccine to Christina's death. In the absence of this predicate showing, an Althen prong 2 analysis is not needed. See Caves, 100 Fed. Cl. at 134. Nevertheless, a brief overview of the evidence particularly relevant to prong 2 is conducted to demonstrate that all the evidence has been reviewed.

A. Prong 2 standards

The Federal Circuit has identified several factors that may be probative with respect to the petitioner's burden on the second prong of Althen. These include, among other things, the opinions of treating physicians, expert testimony, challenge-rechallenge, and pathological markers. See Capizzano, 440 F.3d at 1322.

B. Factors

1. Treating Doctors

The doctor who performed Christina's autopsy, Kari Reiber, was aware that Christina received a third dose of the HPV vaccine a few days before she died.[17]

[17] Dr. Reiber's date of vaccination (June 8, 2008) is not the correct date, which was June 3, 2008. Exhibit 3 at 99.

Dr. Reiber submitted information about Christina's death to the Vaccine Adverse Event Reporting Service (VAERS).

The submission of a VAERS report is not necessarily evidence that the doctor considers the vaccination to have caused the injury being reported. La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 206 n. 37 (2013), aff'd, 746 F.3d 1334 (Fed. Cir. 2014), Vig v. Sec'y of Health & Human Servs., No. 01-198V, 2013 WL 6596683, at *17 (Fed. Cl. Spec. Mstr. Nov. 14, 2013). In addition, Ms. Tarsell did not present any argument based upon either the VAERS report or Dr. Reiber's notation that the HPV preceded Christina's death. See Pet'r's Posth'g Br.; Pet'r's Posth'g Reply Br. Under these circumstances, the opinions of treating doctors do not favor a finding of causation.

2. Challenge-Rechallenge

"A rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." Capizzano, 440 F.3d at 1322. The basic chronology may appear to support a challenge-rechallenge argument. According to Ms. Tarsell's perspective, the following events happened: (1) Christina did not suffer from arrhythmia until she received the first HPV vaccination, (2) the first HPV vaccination caused Christina to suffer arrhythmia, which was detected on the date of the second HPV vaccination, (3) the second HPV vaccination worsened Christina's arrhythmia, and (4) the third HPV vaccination, on June 3, 2008, made Christina's arrhythmia so much worse that she died from it on June 25, 2008.

However, Ms. Tarsell has not presented any argument based upon challenge-rechallenge. The concept does not appear in Ms. Tarsell's pre-trial brief, initial post-hearing brief, or post-hearing reply brief. In addition, Dr. Shoenfeld mentioned challenge-rechallenge only fleetingly. See Tr. 245-46, 257-58, 328-30.

Even if Ms. Tarsell had directly argued challenge-rechallenge, it is not clear that Christina's case fulfills the challenge-rechallenge paradigm. See Nussman v. Sec'y of Health & Human Servs., 83 Fed. Cl. 111, 119-20 (finding special master did not err in rejecting petitioner's argument regarding rechallenge). To start, as discussed extensively in section IV, the onset of Christina's arrhythmia is unknown. She may have had an undetected arrhythmia for many years. If so, the first dose of the HPV vaccination did not cause the arrhythmia. In addition, patients who have an arrhythmia do not follow one clinical course. As Dr. Eldar explained, "somebody has a problem, he lives with it or she lives with it for a

month or years, and then one day, that's it." Tr. 138. In other words, a seemingly benign arrhythmia can become fatal for completely unknown reasons.

3. Response as Predicted by the Causal Theory

The essence of the theories Ms. Tarsell presented is that the HPV vaccination prompted an autoimmune attack on some part of the heart, either the beta adrenergic receptors or the L1 calcium channel. Dr. Phillips explained the implications of these theories:

> If, in fact, it was a significant autoimmune reaction going on, one would expect to see cellular infiltrates in various organs, and if the autoimmune reaction was going on of significance in the heart, you would expect that the myocardium would be infiltrated with lymphocytes.
>
> If there was a cytotoxic antibody there which had been attacking these channels, that cytotoxic antibody would also cause pathologic changes, with secondary infiltration of other cell populations which were inflammatory in nature, including polymorphonuclear cells or mononuclear cells.

Tr. 407-08.

However, what the theories predicted was not found. Doctors from the CDC examined tissue taken during Christina's autopsy. Upon microscopic examination, they reported: "Sections of myocardium show no conspicuous inflammatory cell infiltrates." Exhibit 10 at 170. Ms. Tarsell had no persuasive evidence for this discrepancy.

Consequently, even if Ms. Tarsell had demonstrated the reliability of any theory causally connecting the HPV vaccinations to fatal arrhythmia as an abstract proposition, there is little persuasive evidence that this theory played out in Christina's case.

At the end, we have very little solid information about Christina's unfortunate death. We know that she was Ms. Tarsell's beloved daughter, whose future was bright. We know that her death was entirely shocking and caused Ms. Tarsell a terrible kind of grief.

But, sudden unexpected deaths happen with a greater frequency than may be commonly appreciated. See section I. We do not know the reason why apparently healthy young people die and, in the context of Ms. Tarsell's claim in the Vaccine Program, the Secretary does not bear the burden of supplying a reason for Christina's senseless death. See LaLonde, 746 F.3d at 1340.

VI. Conclusion

Ms. Tarsell claimed that the HPV vaccinations caused Christina's arrhythmia, which led to her death. The evidence was not sufficient to establish the causal relationship between the vaccination and the arrhythmia. Consequently, Ms. Tarsell is not entitled to compensation.

The Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

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