

# In the United States Court of Federal Claims

## OFFICE OF SPECIAL MASTERS

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CHERYL KOEHN,	*	
as mother and next friend of	*	No. 11-355V
VANESSIA KOEHN,	*	Special Master Christian J. Moran
	*	
Petitioner,	*	Filed: May 30, 2013
	*	
v.	*	
	*	Entitlement, HPV vaccine (Gardasil),
SECRETARY OF HEALTH	*	systemic juvenile idiopathic arthritis
AND HUMAN SERVICES,	*	(sJIA)
	*	
Respondent.	*	

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P. Leigh O’Dell, Beasley, Allen, et al., Montgomery, AL, for petitioner;  
Darryl R. Wishard, United States Dep’t of Justice, Washington, DC, for  
respondent.

### **PUBLISHED DECISION DENYING COMPENSATION**<sup>1</sup>

Cheryl Koehn alleges that two doses of the human papillomavirus (“HPV”) vaccine given to her daughter, Vanessa, caused her to suffer from systemic juvenile idiopathic arthritis (“sJIA”).<sup>2</sup> Ms. Koehn seeks compensation from the

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<sup>1</sup> The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. 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.

<sup>2</sup> The Secretary recognized the HPV vaccine as a vaccine covered in the Vaccine Program on April 20, 2007. National Vaccine Injury Compensation  
(. . . continued)

National Childhood Vaccine Injury Compensation Program. 42 U.S.C. § 300aa-10 et seq. (2012). To establish that she is entitled to compensation, Ms. Koehn must fulfill the three-pronged test set forth in Althen v. Sec’y of Health & Human Servs., 418 F.2d 1274, 1278 (Fed. Cir. 2005).

Ms. Koehn relies primarily upon the opinion of Michael McCabe, Ph.D. Dr. McCabe presents an innovative theory involving cytokines to explain how an HPV vaccine can cause sJIA. The Secretary, however, undermined the persuasive value of Dr. McCabe’s hypothesis by presenting a contrary opinion from Carlos Rose, M.D., a board-certified rheumatologist. As detailed in section IV below, Dr. McCabe’s theory has not been tested, has not been the subject of peer-review, is not generally accepted in the relevant medical community, and is inconsistent with epidemiological studies.

The flaws in Ms. Koehn’s evidence extend from the first prong of Althen to the remaining two prongs. Ms. Koehn has not established that the onset of her sJIA occurred in a temporal interval that Dr. McCabe’s theory would predict. See section V. Additionally, Ms. Koehn’s case lacks a “logical sequence of events” that connects her disease to the HPV vaccination as required by the second prong of Althen. See section VI.

Consequently, Ms. Koehn has not established that she is entitled to compensation. A full discussion follows.

## **I. Procedural History**

Ms. Koehn filed her petition on June 6, 2011, and medical records on June 14, 2011. These medical records are summarized in section II.C, below. Ms. Koehn filed a report from Dr. McCabe on August 24, 2011. Exhibit 9. Due to concerns about the adequacy of the disclosure regarding Althen prong one, Ms.

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Program: Addition of Meningococcal and Human Papillomavirus (HPV) Vaccines to the Vaccine Injury Table, 72 Fed. Reg. 19937. Although many petitioners have claimed that the HPV vaccine harmed them, this may be the first instance in which a claim has reached a special master for resolution. (Other HPV vaccine cases have been resolved when petitioners acknowledged that they were not likely to prevail or when the parties reached a settlement.)

Koehn filed a supplemental report from Dr. McCabe on October 3, 2011. Exhibit 27. As discussed more extensively below, in sections II.D.1.b and c, Dr. McCabe opined that the HPV vaccine caused Vanessa's sJIA. Ms. Koehn also filed the articles on which Dr. McCabe relied.

After Ms. Koehn made these submissions, the Secretary evaluated the evidence. The Secretary recommended that compensation be denied because Ms. Koehn had not satisfied any of the three elements set forth in Althen. In addition to identifying perceived flaws in Dr. McCabe's opinion, the Secretary also relied upon an opinion presented by Dr. Rose. Resp't Rep't, filed Nov. 14, 2011. The gist of Dr. Rose's opinion is that there is not adequate evidence to support the theory that the HPV vaccine can cause sJIA. See sections II.D.2.b and c, below.

The parties did not succeed in resolving the case through a settlement. Thus, the case was set for a hearing. In advance of the hearing, the parties filed briefs and additional medical literature. Dr. McCabe and Dr. Rose testified at a hearing held on June 21, 2012. Following the hearing, the parties submitted additional articles and briefs.

Ms. Koehn's claim that the HPV vaccine caused Vanessa's sJIA is ready for adjudication. The foundational elements—the HPV vaccine and sJIA—are discussed first. The following sections review Vanessa's medical history as well as the qualifications, reports, and testimony of the experts. After a short recitation of the legal standards, this decision separately analyzes Ms. Koehn's evidence for each of the Althen prongs. Section VII provides the conclusion.

## **II. Background**

To provide context to Vanessa's medical history and the opinions of the parties' experts on the issue of vaccine causation, found below in sections II.C and D, respectively, it is helpful first to review some preliminary information concerning the vaccine Vanessa received and the condition from which she suffers. Thus, sections II.A and B provide a brief overview of human papillomavirus, HPV vaccine, and JIA.

## **A. Human Papillomaviruses and Human Papillomavirus Vaccines**

### **1. Human Papillomaviruses**

There are more than 130 different types of human papillomaviruses. These viruses tend to be found in cutaneous or mucosal epithelial surfaces. Some strains of human papillomavirus are relatively benign, causing warts. Other strains, in particular HPV 16 and HPV 18, cause cervical cancer. Exhibit 16 (Margaret Stanley, Immunobiology of HPV and HPV vaccines, 109 *Gynecologic Oncology* S15 (2008)) at S15-16.

Because of the cells that it infects, a human papillomavirus “is practically invisible to the host who remains ignorant of the pathogen for long periods of time.” A human papillomavirus does not cause cytolysis,<sup>3</sup> necrosis,<sup>4</sup> or inflammation. Without exposure to the host’s immune system, “there is little or no release into the local milieu of pro-inflammatory cytokines.” Id. at S16. This is part of the virus’s strategy for survival.

Given enough time, “most [human papillomavirus] infections resolve.” But, approximately 10-20 percent of infected individuals develop persistent infections. One reason appears to be that humans produce relatively few antibodies in response to the human papillomavirus. Id. at S17.

### **2. Vaccines against Human Papillomaviruses**

Developing an effective vaccine against human papillomaviruses was challenging, in part, because of the need to generate a robust response from the person’s immune system. Exhibit 16 (Stanley) at S17-18. Researchers eventually succeeded in creating an HPV vaccine that induces “high concentrations of neutralizing antibodies.” Id. at S18. An HPV vaccine can cause the host to produce more antibodies than the human papillomavirus because, in part, the vaccine is given intramuscularly, close to the lymph nodes. This delivery system

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<sup>3</sup> Cytolysis is the “destruction of a cell by rupture of the cell membrane with loss of cytoplasm.” Dorland’s Illustrated Medical Dictionary 466 (32nd ed. 2012).

<sup>4</sup> Necrosis is “the sum of morphological changes indicative of cell death.” Dorland’s at 1235.

“circumvent[s] the immune avoidance strategies of the viral intraepithelial infectious cycle.” Id.

### a) HPV Vaccine Composition

Another advance in the creation of vaccines against the human papillomavirus was the reproduction of a portion of the virus known as the L1 protein. The resulting virus-like particle (VLP) stimulates the immune system to produce antibodies and the antibodies confer immunity to the particular strand of the human papillomavirus. Exhibit 17 (Margaret Stanley, HPV- immune response to infection and vaccination, 5 *Infectious Agents & Cancer* 19 (2010)) at 2-3. There are two different vaccines against human papillomavirus. One, known as Cervarix, contains the L1 VLP for two strands, 16 and 18. The other, known as Gardasil, contains the L1 VLP for four strands, 6, 11, 16, and 18. Id. at 3. In addition to the difference in strands, Cervarix and Gardasil contain different adjuvants.<sup>5</sup> Cervarix uses an adjuvant known as AS04, which is comprised of a lipid and an aluminum salt. Exhibit E (Thomas Verstraeten et al., Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines, 26 *Vaccine* 6630 (2008)) at 6631. On the other hand, Gardasil uses amorphous aluminum hydroxyphosphate sulfate to increase antibody production. Transcript (“Tr.”) 154; Physician’s Desk Reference at 1828 (66th ed. 2012).

### b) HPV Vaccine Effectiveness

Experiments on HPV vaccines have shown that “the peak geometric mean antibody concentrations achieved are at least two [logarithmic] higher than those after natural seroconversion”<sup>6</sup> and for “the majority of vaccinated subjects, serum antibody levels remain at concentrations greater than those found in natural infection.” Exhibit 16 at S18. One article commented that “[i]t is fairly uncommon that a vaccine will produce an immune response greater than that

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<sup>5</sup> An adjuvant is a stimulator of a more robust immune response. See Dorland’s at 32

<sup>6</sup> Seroconversion is “the change of a patient’s serologic test from negative to positive, indicating the development of antibodies in response to infection or immunization.” Dorland’s at 1698.

achieved by natural infection.” Exhibit 21 (Villa et al., Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18, 24 Vaccine 5571 (2006)) at 5581.<sup>7</sup>

The amount of time to generate the antibody response was discussed in several articles. For example, one article reported that “vaccination induced a marked immune response, beginning approximately 1 month after the initial dose, peaking at approximately month 7, and thereafter declining to a stable plateau for 2.5 years after the last vaccine dose.” Exhibit 25 (Ian Frazer, Correlating immunity with protection for HPV infection, 11 Int’l J. Infectious Diseases S10 (2007)) at S13; see also exhibit 22 (Elmar Joura et al., HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine, 26 Vaccine 6844 (2008)) at 6849; exhibit 28 (Alfonso García-Piñeres et al., Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles, 14 Clinical & Vaccine Immunology 984 (2007)) at 986; exhibit 29 at 331.

In addition to looking at the production of antibodies in response to an HPV vaccine, researchers have also investigated the cytokine response. E.g., exhibit 28 (García-Piñeres), exhibit 32 (Rebecca T. Emeny et al., Priming of Human Papillomavirus Type 11-Specific Humoral and Cellular Immune Responses in College-Aged Women with a Virus-Like Particle Vaccine, 76 J. Virology 7832 (2002)), exhibit 30 (Thomas G. Evans et al., A Phase 1 Study of a Recombinant Viruslike Particle Vaccine against Human Papillomavirus type 11 in Healthy Adult Volunteers, 183 J. Infectious Diseases 1485 (2001)). At the hearing, relatively little attention was paid to the García-Piñeres article, Emeny article, or the Evans article because Dr. McCabe and Dr. Rose primarily discussed an article by Pinto. See, e.g., Tr. 119-20.

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<sup>7</sup> Other studies that also reported that the vaccine produces a stronger antibody response include exhibit 29 (Ligia A. Pinto et al., Cellular Immune Responses to Human Papillomavirus (HPV)—16 L1 in Health Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles, 188 J. Infectious Diseases 327 (2003)) at 336; exhibit 35 (Purnima Bhat et al., Regulation of immune responses to HPV infection and during HPV-directed immunotherapy, 239 Immunological Revs. 85 (2011)) at 87; and exhibit 18 (Luciano Mariani & Aldo Venuti, HPV vaccine: an overview of immune response, clinical protection, and new approaches for the future, 8 J. Translational Med. 105 (2010)) at 107.

Dr. McCabe bases much of his opinion on the Pinto article, which, according to Dr. McCabe, is “an important paper in vaccinology, the study of vaccines.” Tr. 100. The Pinto study is “a technical tour de force.” Tr. 100, 103. Therefore, due to its complexity and its significance, the Pinto article is reviewed in detail.

When this study was conducted, vaccines against human papillomavirus were being developed. Dr. Pinto and colleagues designed an experiment “to better characterize the innate and acquired immune system cytokine response elicited by L1 VLP vaccination.” Exhibit 26 (Ligia A. Pinto et al., HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood, 23 Vaccine 3555 (2005)) at 3556. The vaccination referenced in the Pinto article contained one protein present in Gardasil. Tr. 100.

Twenty-four women participated in the study. Blood specimens were collected before the initial injection, known as month zero. Twenty women, then, received a 50 µg dose of vaccination without adjuvant and four women received a placebo of sterile saline solution. One month later, all women were given a second injection of the same substance (either the vaccination or a placebo). At month two, more blood was drawn. At six months, the women received a third injection. At seven months, more blood was drawn. Exhibit 26 at 3556.

The researchers determined the level of cytokines for each of the three blood samples after different types of stimulation. Exhibit 26 at 3557. This process was done “in vitro,” id. at 3562, meaning in glass, like a test tube. Dorland’s at 956. The blood from women who received the vaccine and women who received the placebo was evaluated in the context of four substances. In the first, the blood was not stimulated at all. The researchers refer to this as the “media.” In the second, the blood was stimulated with 10 µg of the virus-like particle present in the vaccine. In the third, the blood was stimulated with 1.0 µg of the virus-like particle. In the fourth, the blood was stimulated with a control known as PHA. Exhibit 26 at 3557, § 3.1; see also Tr. 292-93. The stimulation was for “24 [hours] in the absence or presence of L1 VLP or PHA.” Exhibit 26 at 3559 (caption to figure 1).

As discussed below in section IV.B.3, the researchers obtained different results depending upon whether there was any stimulation. For cells in the media—meaning no stimulation—the cytokine levels stayed relatively similar from month zero to month two to month seven. “As shown in Fig. 1D, spontaneous secretion of cytokines in the absence of any stimuli (media control)

did not show any significant increases following vaccination.” Exhibit 26 at 3560. For blood that was stimulated either with 10 µg or 1.0 µg of the virus-like particle, cytokines increased. “Stimulation of cells from vaccine recipients with L1 VLP (10 µg/ml) induced significant increases in the median levels of inflammatory . . . cytokines.” Id. at 3557-59. “Similar patterns of cytokine production to the ones seen in response to L1 VLP at 10 µg/ml were observed when L1 VLP was tested at 1.0 µg/ml.” Id. at 3559.

### c) HPV Vaccine Safety

Dr. McCabe and Dr. Rose each referenced one epidemiological study that investigated the safety of an HPV vaccine.<sup>8</sup> One was an article by Chun Chao. Exhibit 34 (Chao et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine, 271 J. Intern. Med. 193 (2012)). The other was an article by Thomas Verstraeten. Exhibit E.

#### (1) Chao Article

Dr. Chao and colleagues used a database to look at the medical history of nearly 190,000 women. Their goal was to determine whether women who received a dose of a quadrivalent human papillomavirus vaccine developed autoimmune diseases within 180 days after the vaccination. Exhibit 34 at 193. The researchers selected 180 days “to accommodate lag time for clinical work” necessary for the treating doctor to arrive at the correct diagnosis. Id. at 201.

The article says that the researchers looked for cases of “juvenile rheumatoid arthritis (JRA).” Id. at 194. The article explained how the researchers looked for various diseases:

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<sup>8</sup> Dr. Rose also reproduced a portion of the package insert (also known as the manufacturer’s label). See exhibit A at 3-4. The Secretary, however, did not submit the package insert as an exhibit, did not ask any questions about the package insert during direct examination of Dr. Rose, and did not cite it in her post-hearing brief. Although Ms. Koehn asked some questions about the package insert during the cross-examination of Dr. Rose, Tr. 252-60, the package insert does not affect the outcome of this case.

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 of an autoimmune condition. To this end, ICD-9 diagnosis codes, abnormal laboratory results or pharmacy prescriptions possibly indicative of autoimmune conditions . . . were captured.

Id. at 194-95. Information about the specific ICD-9 codes was contained in Appendix A-C. Id. at 195. However, the copy of the Chao article that was filed as exhibit 34 did not contain the appendices. See exhibit 34.

After the scope of the case ascertainment became an issue at the hearing, see Tr. 248, Dr. Rose was permitted to file the relevant appendix and a report commenting on the ICD-9 code. As a preliminary matter, Dr. Rose explained what an ICD-9 code is:

The ICD-9 is a complex and evolving international coding system utilized by patient care providers to identify the condition or conditions suffered by their patients. The codes have a multiplicity of uses including retrospective identification of cases for public health projects (like the one in question), utilization of resources, quality assurance and adequacy of charges for rendered services.

Exhibit I (Dr. Rose’s supplemental report, dated Nov. 1, 2012) at 2.<sup>9</sup> Dr. Rose next stated that under the ICD-9, the relevant code is 714.3, juvenile rheumatoid arthritis. Id. The Chao researchers used this code. See exhibit H (reproduction of Appendix A-1 from the Chao article). In addition, the Chao researchers also searched for medications commonly prescribed for sJIA. Exhibit I at 3. Thus, Dr. Rose concluded that “almost certainly all cases of JRA within the study population would have been detected with the methodology utilized by the investigators.” Id. at 4.

Given this understanding of what the researchers did, the results can be stated. In the category of juvenile rheumatoid arthritis, the researchers found three

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<sup>9</sup> For more information about ICD-9 codes, see Fresco v. Sec’y of Health & Human Servs., No. 06-469V, 2013 WL 364723, at \*9 n.40 (Fed. Cl. Spec. Mstr. Jan. 7, 2013).

cases arising after vaccination. Exhibit 34 at 197 (table 1, column E, line 6). Among people who were not vaccinated, the researchers estimated that there were 43 cases. *Id.* at 199 (table 3, third column, line 6). The incidence rate ratios (“IRR”) was 0.48 with a 95% confidence interval of 0.26-0.91. *Id.* (table 3, columns 4-5, line 6). Dr. Rose explained that because the confidence interval was below 1.0, there was “no increase in risk of developing new onset of JRA after HPV vaccination.” Exhibit I at 3. Although Dr. Chao and colleagues did not make a specific finding for juvenile rheumatoid arthritis, their overall conclusion was similar. They stated that “this observational surveillance study offers some assurance that amongst a large and likely generalizable female population, no safety signal for autoimmune conditions was found following HPV4 vaccination in routine clinical use.” *Id.* at 202.

## (2) Verstraeten Article

The Verstraeten article collects several studies about the safety of vaccines containing an adjuvant known as AS04. AS04 is the adjuvant in Cervarix, not the adjuvant used in Gardasil. Exhibit E at 6631; Tr. 240 (Dr. Rose).

Dr. Verstraeten’s and colleagues’ goal was “to evaluate the safety of AS04 adjuvanted vaccines with regard to rates of AEs [adverse events] of potential autoimmune aetiology.” Exhibit E at 6631. To address the problem that small studies may not detect rare events, Dr. Verstraeten and colleagues collected “[a]ll completed or ongoing controlled, randomised studies of AS04 adjuvanted HPV-16/18, HSV and HBV vaccines conducted by GSK Biologicals [GlaxoSmithKline, the manufacturer of those vaccines] or collaborators,” with one exception. *Id.* Forty-two studies were included. *Id.* at 6632 (table 1). More than 36,000 people received a vaccine and more than 30,000 people served as controls. *Id.* In regard to the number of people, Dr. Rose stated that the Verstraeten article was “the closest that we can be to an epidemiological study” because it studied “about 60,000 individuals . . . [and] covered two years of followup.” Tr. 232. Dr. McCabe did not address this article.

Using a database, Dr. Verstraeten and colleagues looked for adverse events following the vaccination using terms in the Medical Dictionary for Regulatory Activities. Exhibit E at 6631. One of the terms was “juvenile arthritis,” which,

according to Dr. Rose, encompasses sJIA. *Id.* at 6633 (table 2); Tr. 287.<sup>10</sup> The authors' general conclusion was their study "did not show evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04 compared with controls." Exhibit E at 6633.

## **B. Juvenile Idiopathic Arthritis**

### **1. Basic Information<sup>11</sup>**

The term "juvenile idiopathic arthritis" encompasses several different diseases. The form affecting Vanessa is known as sJIA.<sup>12</sup> The diagnostic criteria

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<sup>10</sup> Another term was "rheumatoid arthritis," an autoimmune disease that Dr. Rose stated does not encompass sJIA. Exhibit E at 6634 (table 3); Tr. 287; see also Tr. 186, 197-98. Among the vaccine recipients, there were 12 cases of rheumatoid arthritis. Among the controls, there were nine cases. Exhibit E at 6634 (table 3). The relative risk was 1.17 and the 95 percent confidence interval ranged from 0.47 to 2.86. *Id.* at 6635 (table 4). When asked about this article, Dr. McCabe explained that a relative risk of greater than one means that the risk is increased and a relative risk of less than one means that the risk is decreased. Tr. 188.

<sup>11</sup> Dr. McCabe, who is not a medical doctor, testified that he learned more about sJIA by reading articles about the disease in the course of preparing his expert report. Tr. 164; see also Tr. 65 (discussing exhibit 12), 75-80 (discussing exhibit 13). Dr. Rose, who is a pediatric rheumatologist with experience in treating sJIA, generally did not challenge the accuracy of information provided about the disease. Thus, the source of information about sJIA is the set of articles filed as exhibits as well as the testimony.

<sup>12</sup> Other names for this same entity include Still's disease, systemic arthritis, systemic-onset juvenile rheumatoid arthritis, and systemic-onset juvenile chronic arthritis. Exhibit C (Fabrizio De Benedetti & Rayfel Schneider, Chapter 14: Systemic Juvenile Idiopathic Arthritis, in Textbook of Pediatric Rheumatology ("Textbook") (James T. Cassidy et al. eds., 6th ed. 2011)) at 236. Exhibit G contains a photocopy of the cover of this textbook, the book's publication information, and the first page (page 236) of chapter 14. For ease, all citations to this textbook will be made to exhibit C.

include: arthritis and a quotidian fever<sup>13</sup> for at least two weeks, plus a rash, lymphadenopathy, enlargement of the liver or spleen, or serositis. Exhibit C at 236 (relying upon the criteria set by the International League of Associations for Rheumatology).

The disease manifests in different parts of the body. Characteristically more than one joint is affected. During active inflammation, a person often experiences muscle pain, a fever and rash. The disease also causes problems in the person's spleen and lymph nodes. Less common features include problems in the heart, liver and (more rarely) the central nervous system. Exhibit C at 238-41.

“The acute manifestations of sJIA are variable in duration and last from weeks to months.” Id. at 246. While approximately 40 percent of patients nearly completely recover after one course of the disease, more than half of the people afflicted “have a persistent disease course.” Id. In the United States, less than 0.5 percent of people with sJIA die from it. Id. at 247.

Treatments for sJIA include “medications to minimize joint inflammation.” Id. at 244. Prednisone is recommended.<sup>14</sup> Other drugs that have some effectiveness include anti-tumor necrosis factor,<sup>15</sup> anti-interleukin 6 receptors, anti-interleukin 1, methotrexate,<sup>16</sup> intravenous immunoglobulin, cyclosporine-A, and thalidomide. Exhibit C at 244-46.

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<sup>13</sup> A quotidian fever is one that “recurs every day.” Dorland's at 693. The fever in sJIA is also sometimes referred to as a “hectic fever,” which also means recurring each day. Id. at 692.

<sup>14</sup> Prednisone is a medication against inflammation and suppresses the immune system. Dorland's at 1509.

<sup>15</sup> An example of a pharmaceutical that inactivates tumor necrosis factor is etanercept. Dorland's at 650. Enbrel is a trademarked name for etanercept. Id. at 612.

<sup>16</sup> Methotrexate is a “folic acid inhibitor” used for many conditions, including “severe rheumatoid and psoriatic arthritis.” Dorland's at 1151.

Studies from Europe suggest that sJIA has an annual incidence of between 0.3 and 0.8 per 100,000 children less than 16 years of age.<sup>17</sup> Although the onset peaks among children 1-5 years old, adolescents and adults can also develop the disease. Males and females are affected equally. Id. at 236.

## 2. Causes

The term name of the disease—systemic idiopathic juvenile arthritis—provides information about what is known about the cause of the disease. According to a medical dictionary, “idiopathic” means “of unknown cause or spontaneous origin.” Dorland’s at 912. “Idiopathic” does not mean that there is no cause. While the cause or causes of sJIA have not been found, “there is substantial evidence of a dysregulated innate immune response with consequent increased production of inflammatory cytokines.” Exhibit G at 237.<sup>18</sup>

Cytokines are “nonantibody proteins released by one cell population . . . on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response.” Dorland’s at 466. Cytokines are “the ways we tell one cell to the other what to do.” Tr. 279 (Dr. Rose). Cytokines are “very ubiquitous” and the cytokine response is “almost . . . universal.” Id. After a person encounters an antigen, the immune system responds with the production of cytokines within hours. Tr. 281-82 (Dr. Rose), 295, 300 (Dr. McCabe).

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<sup>17</sup> The incidence rate refers to the number of new cases in a population over a period of time. See Dorland’s 1595.

<sup>18</sup> An autoinflammatory disease differs from an autoimmune disease. See Dorland’s at 181 (defining autoimmune and autoinflammatory). Autoimmune diseases, about which special masters often hear testimony, are caused by autoantibodies and autoreactive T cells. However, in sJIA, autoantibodies and autoreactive T cells are not involved. Thus, sJIA is not an autoimmune disease. Exhibit 13 (Elizabeth D. Mellins et al., Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions, 7 *Nature Revs. Rheumatology* 416 (2011)) at 417-18.

While rheumatologists such as Dr. Mellins, distinguish autoimmune diseases from autoinflammatory diseases, Dr. Chao and Dr. Verstraeten (two epidemiologists) did not maintain this precision. Although both articles discuss “autoimmune diseases,” that phrase is broad enough to include sJIA. See section II.A.2.c.

Human beings produce a finite number of types of cytokines, with perhaps as many as 40 different cytokines being identified so far. Tr. 290; see also Tr. 172 (Dr. McCabe stating he “accept[s] to a certain extent that there is a commonality in immune effector functions”). Depending on the context, cytokines have different purposes. Some cytokines promote inflammation while other cytokines are anti-inflammatory. See Tr. 78. Dr. McCabe stated that ordinarily, pro-inflammatory cytokines can act on multiple tissues and can lead to (a) increased vascular permeability, (b) fever, and (c) increased synovial inflammation. Tr. 77-78; see also exhibit 13 (Mellins) at 418-21, reproduced as exhibit 38 (PowerPoint slides) at 5.

The specific pro-inflammatory cytokines that have been implicated in the development of sJIA include interleukin (“IL”) 1, IL-6, IL-7, IL-8, IL-18, macrophage inhibitory factor, and tumor necrosis factor. Exhibit C (Textbook) at 237; Tr. 66 (Dr. McCabe), 280 (Dr. Rose). “Many features of sJIA seem to be explained by the known effects of innate proinflammatory cytokines, IL-1 and IL-6 in particular.” Exhibit 13 at 418.

How any of these cytokines contribute to sJIA is unknown.<sup>19</sup> As one textbook stated, “[t]he role of each one of these mediators is far from being clarified.” Exhibit C at 237. At the hearing, Dr. McCabe recognized that the medical community did not understand what the cytokines were doing at the cellular level. Tr. 299.

Even accepting the proposition that pro-inflammatory cytokines contribute to the course of sJIA, this observation does not identify the causes of the disease because something must initiate the increase in cytokines. Hence, one of the articles cited by Dr. McCabe asks “What are the initial triggers of sJIA?” Exhibit 13 (Mellins) at 423. As Dr. Rose explained, medical researchers are generating

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<sup>19</sup> The production of pro-inflammatory cytokines does not always result in disease. In fact, as Dr. McCabe and Dr. Rose recognize in their expert reports, the production of pro-inflammatory cytokines is a protective response that vaccines are designed to elicit. See exhibit 9 (Dr. McCabe) at 3 and exhibit A (Dr. Rose) at 6; see also exhibit 26 (Pinto). The production of these pro-inflammatory cytokines, however, is associated with diseases, including diseases other than sJIA, such as sarcoidosis and systemic lupus erythematosus. Tr. 279.

hypotheses to explain the development of pro-inflammatory cytokines. See Tr. 217.

Dr. McCabe identified three articles in which the authors stated that infections or vaccinations could be the initial cause for sJIA. Tr. 136, 142-43, 145-46. One article stated, “in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares hint[s] at a possible relation of JIA disease activity and vaccinations or infections.” Exhibit 15 (Arash Ronaghy et al., Vaccination leads to an aberrant FOXP3 T-cell response in non-remitting juvenile idiopathic arthritis, 70 Ann. Rheum. Dis. 2037 (2011)) at 1<sup>20</sup> (footnote deleted without notation). Another article asserted that “[o]ne scenario is that infectious agents that are typically encountered in childhood initiate sJIA; no single environmental trigger has been identified, although this lack of an obvious candidate could point to multiple common agents being capable of initiating sJIA.” Exhibit 13 (Mellins) at 417. A third article stated “[i]n juvenile idiopathic arthritis, infections and vaccinations have been suggested as two candidate triggers.” Exhibit 12 (Berent Prakken et al., Juvenile idiopathic arthritis, 377 Lancet 2138 (2011)) at 2141. This article continued, “but neither has been confirmed as a trigger because of a scarcity of proper controlled, prospective studies.” Id.

In the context of discussing vaccination as a possible trigger, Prakken cited two articles that were filed into the record. Exhibit 12 (Prakken) at 2141 nn. 46, 47. In both studies, the people given the vaccine already suffered from juvenile idiopathic arthritis and the researchers were examining whether the patient’s disease worsened after the vaccination. One study involved the mumps, measles, and rubella (“MMR”) vaccine. In a retrospective analysis of 207 patients with juvenile idiopathic arthritis (of which 17 had systemic arthritis), the researchers found “no changes in disease activity, flare occurrence or medication use after the MMR vaccination.” Exhibit 43 (Marloes W. Heijstek et al., Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis, 66 Ann. Rheum. Dis. 1384 (2007)) at 1386. Thus, the researchers concluded that the “MMR vaccination appears to be safe in JIA.” Id.

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<sup>20</sup> This article, as submitted, does not have the same pagination as originally published in the Annals of Rheumatic Diseases.

The other study used the meningococcal C vaccination. The total number of participants was 234, including 34 with systemic arthritis. The researchers “did not detect any worsening of disease activity within 6 months after MenC vaccination.” Exhibit 47 (Evelien Zonneveld-Huijssoon et al., Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis, 56 *Arthritis & Rheumatism* 639 (2007)) at 644.

The parties did not submit any case reports linking the Gardasil vaccine and JIA.

### **C. Vanessa’s Medical History before and after her sJIA Diagnosis<sup>21</sup>**

Vanessia was born in February 1995. She was generally healthy for the first 12 years of her life. In February 2008, Vanessa saw her regular doctor, Dr. Elena R. Regala for a routine check-up. Dr. Regala noted Vanessa’s history of asthma. Exhibit 3 at 11. Dr. Regala’s office administered the first dose of the HPV vaccine to Vanessa on this date. Id.; exhibit 2 at 3. Vanessa received the second dose of the HPV vaccine on April 18, 2008. Exhibit 2 at 3; exhibit 3 at 8.

On approximately June 21, 2008, Vanessa developed a rash all over her body. She reported to Dr. Regala on June 24, 2008, that she had this rash for “3 days.” Exhibit 3 at 8. Dr. Regala suspected an allergic reaction and prescribed Benadryl and prednisone. Id. The rash disappeared in three days. Id. at 26 (notes dated July 2, 2008).

Vanessia stopped taking the prednisone and, on June 27, 2008, she developed pain in many places including her knees, thighs, and calves. Exhibit 4 at 14.<sup>22</sup> Dr. Regala’s impression included juvenile rheumatoid arthritis. Exhibit 3 at 27.

On June 28, 2008, Vanessa was admitted to Marian Medical Center for “high fever accompanied by severe joint pains of the knees and ankles,” which

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<sup>21</sup> The parties accept the accuracy of the medical records.

<sup>22</sup> Given that Dr. Regala prescribed prednisone on June 24, 2008, and Vanessa reported, on June 27, 2008, that she had stopped taking prednisone, it appears that Vanessa actually took prednisone for fewer than three days.

started on June 25, 2008. Exhibit 3 at 26. While in the hospital, various laboratory tests were done. Exhibit 3 at 12-21; exhibit 4 at 6. Dr. Frank Scott, a rheumatologist, saw Vanessa. Dr. Scott's impression was that she had "probable Still's disease (systemic onset juvenile arthritis)." Exhibit 4 at 11-12. Vanessa was prescribed prednisone. By the day on which she was discharged (July 2, 2008), she had started to feel better, no longer had a fever, and was not suffering from joint pains. However, she still had a rash. When she left the hospital, her presumptive discharge diagnosis was JIA. Exhibit 4 at 6. At discharge, Dr. Regala referred Vanessa to a pediatric rheumatologist. Exhibit 3 at 11.

On July 8, 2008, Vanessa saw Dr. Deborah McCurdy, a pediatric rheumatologist at the University of California at Los Angeles Health System. Dr. McCurdy recorded that Vanessa's vaccinations were up-to-date, including a second dose of the HPV vaccine. Dr. McCurdy also noted that Vanessa's family history included JIA. Exhibit 5 at 51. Dr. McCurdy stated that Vanessa's symptoms made "sJIA very likely." *Id.* at 55. Dr. McCurdy continued the prescriptions for prednisone and was waiting for the results of pending laboratory studies to add methotrexate and Enbrel. *Id.* Dr. McCurdy sent a letter summarizing her findings to Dr. Regala on July 8, 2008. Exhibit 5 at 20-26. Dr. McCurdy's letter mentioned that Vanessa had "just received the second of three HPV vaccines." *Id.* at 21.

Vanessia saw Dr. Regala again on August 19, 2008. Exhibit 3 at 6. Dr. Regala knew that Vanessa was suffering from JIA from the previous correspondence with Dr. McCurdy. See exhibit 5 at 20, 24 (Dr. McCurdy's letter to Dr. Regala dated July 8, 2008). Dr. Regala administered the third dose of the HPV vaccine to Vanessa on August 19, 2008. Exhibit 3 at 6; see also exhibit 2 at 3.

On August 27, 2008, a physical therapist associated with a local public health department, Sylvia Medinger, saw Vanessa in response to a referral from Dr. McCurdy. In her history, Ms. Medinger recorded that Vanessa's dose of prednisone had ended on August 18, 2008. Vanessa was still receiving Enbrel. On August 25, 2008, Vanessa had a "flare-up . . . with fever, rash and increase in pain." Ms. Medinger evaluated Vanessa and recommended that she have physical therapy twice a week. Exhibit 8 at 48-50.

Vanessia returned to Dr. McCurdy on September 3, 2008. Vanessa recounted that she was having some symptoms after stopping prednisone. Dr. McCurdy recorded that Vanessa had "some improvement with Enbrel." Vanessa

was also taking methotrexate. Dr. McCurdy examined Vanessa and found that she had swollen knees and ankles. Dr. McCurdy's impression was that she was "improved but still [had evidence of] active [disease]" and was "better." Exhibit 5 at 45-46.

Dr. McCurdy continued to care for Vanessa and follow-up appointments were held in December 2008, 2009 (two appointments), and 2010. At these visits, Vanessa, despite her JIA, was generally "doing well." The doctors recommended that she receive the influenza vaccine and H1N1 vaccine. Exhibit 5 at 32, 41, 44, 60.

Another follow-up appointment occurred on January 12, 2011, at UCLA. This time, Vanessa saw Dr. Alice Hoftman, another pediatric rheumatologist. Dr. Hoftman's record states that Vanessa was "currently pursuing lawsuit against Gardasil. [Received] Gardasil #2, 4/08. [Diagnosed] 7/08." Exhibit 5 at 27. During this visit, Dr. Hoftman apparently recommended that Vanessa receive the flu vaccine. Despite having previously accepted the doctor recommendation that Vanessa receive a flu vaccine in 2008-2010, Ms. Koehn refused at this visit. See exhibit 5 at 28, 32 (H1N1 vaccine), 44, 60. Regarding her refusal, Dr. Hoftman wrote: "[patient's] mother refused flu vaccine this year. Discussed [with] mom the importance of this vaccine. Mom hesitant [because] Gardasil. [Discussed with] mom – no data but all vaccines and infections can trigger autoimmune response." Id. at 28.

## **D. Experts' Qualifications, Reports and Testimony**

### **1. Petitioner's Expert, Michael J. McCabe, Ph.D.**

#### **a) Qualifications**

Dr. McCabe earned a Ph.D. in microbiology and immunology from Albany Medical College in 1991. He worked at the Karolinska Institute in Stockholm, Sweden as a postdoctoral research associate from 1990 to 1992. In 1992, he joined the faculty of Wayne State University as a research assistant professor at the Institute of Chemical Toxicology. His research explored how chemicals, metals and other contaminants from the environment affect the immune response. He also held various other positions at Wayne State University until 2000. Exhibit 10 (curriculum vitae); Tr. 12-14, 50-53.

From 2000 to 2009, Dr. McCabe worked, first as an assistant professor and then as an associate professor, in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. Dr. McCabe's duties included research, a small amount of teaching, and administration. While supervising approximately 25 scientists "working on lab-based and epidemiological research projects," Dr. McCabe's research focused on "mechanistic metal toxicology and immunotoxicology." Exhibit 10; see also Tr. 15-17, 35-37 (detailing teaching responsibilities).

In 2009, Dr. McCabe started working at Robson Forensic, Inc. as an associate. In that capacity, Dr. McCabe provides "reports and testimony toward the resolution of . . . personal injury litigation of toxicology and human health assessments involving environmental and occupational exposures to agents such as metals." Exhibit 10; see also Tr. 33-34.

Dr. McCabe has written about 40 articles that appear in peer-reviewed publications and about 12 book chapters. Most, but not all, of Dr. McCabe's publications relate to the toxicity of metals. Tr. 15, 37-39.

Dr. McCabe has contributed to select committees exploring causation. For example, Dr. McCabe participated on a National Academy of Science committee exploring beryllium alloy exposure. He reviewed proposals about Gulf War injuries for the Department of Defense. He was a co-author of a white paper about the role of the environment in developing autoimmune diseases for the National Institute of Environmental Health Sciences. Exhibit 10; Tr. 22-29.

In response to questions asked by the Secretary's counsel during voir dire, Dr. McCabe stated that he is not a medical doctor and does not treat patients. Tr. 33. He has not researched sJIA. Tr. 41. However, Dr. McCabe has been involved in a small pilot study, examining how "lead-intoxicated girls" responded to Gardasil. Tr. 42.

His current position at Robson Forensics, Inc. requires him to "review legal cases, produce reports, and testify as needed." Tr. 33. Dr. McCabe estimated that activities related to litigation provide more than 95 percent of his income with most of his work for plaintiffs. Tr. 33-34.

Ms. Koehn offered Dr. McCabe as an expert in the field of immunology to which the Secretary did not interpose an objection. Tr. 31, 50. Dr. McCabe was recognized as an expert in immunology. Tr. 53.

## b) Report<sup>23</sup>

Dr. McCabe's report begins with a review of Vanessa's medical history. Dr. McCabe's recitation is consistent with the information presented above.

Dr. McCabe describes "juvenile rheumatoid arthritis."<sup>24</sup> He emphasizes that this disease is an autoinflammatory process "driven by dysregulation of the innate immune system as evidenced by a role for pro-inflammatory cytokines (e.g. IL-6, IL-1 and TNF- $\alpha$ )." Exhibit 27 at 2. He states, "[m]uch as the same with most human autoimmune diseases, the cause of Juvenile Rheumatoid Arthritis is thought to be multifactorial – with genetic susceptibility factors and environmental triggers working together in complex ways to initiate and perpetuate adaptive and innate immune activities resulting in tissue damage." *Id.* at 2-3. "[T]he basis for the argument for a causative role for these environmental triggers [referring to infections and vaccinations] comes from mechanistic considerations." *Id.* at 3.

Dr. McCabe also describes the HPV vaccine. Citing an article by Pinto, Dr. McCabe asserts that "[i]n individuals immunized with [HPV vaccines], high levels of both adaptive and innate immune cytokines are produced." *Id.* at 3. "Notably, many of these same vaccine-elicited cytokines are the pro-inflammatory cytokines that have been implicated in the etiology of JRA." *Id.* As made clear during the hearing, this is the essence of Dr. McCabe's theory: an HPV vaccine elicits a certain cytokine pattern (particularly IL-6) and these cytokines cause sJIA. Tr. 123.

Dr. McCabe's report also elaborates on the topic of the temporal interval that is medically appropriate for causation. Dr. McCabe cites studies that showed that within seven months of Gardasil vaccination, more than 99 percent of people have seroconverted. Exhibit 27 at 4-6. This discussion implies that it was appropriate to infer that development of a disease within seven months of a vaccination was caused by the vaccination.

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<sup>23</sup> Dr. McCabe's supplemental report encompasses his original report. Therefore, citations will be only to the report dated October 1, 2011 (Exhibit 27).

<sup>24</sup> Dr. Rose pointed out that "juvenile rheumatoid arthritis" is not the currently preferred term. Exhibit A at 4-5.

### c) Testimony<sup>25</sup>

After presenting his qualifications, Dr. McCabe discussed Gardasil. Tr. 54-55. He summarized Vanessa's medical history, Tr. 55-61, and his synopsis is in accord with the findings of fact set forth above. Dr. McCabe premised his opinion on Vanessa's diagnosis of sJIA. Tr. 60.<sup>26</sup>

Dr. McCabe's next topic was explaining how Gardasil can cause sJIA. Dr. McCabe began by explaining a prevailing theory of how sJIA originates. As mentioned above in section II.B., sJIA is mediated by pro-inflammatory cytokines, such as TNF, interleukin 1, interleukin 6, and interleukin 18. The role of these pro-inflammatory cytokines leads to a classification of sJIA as an autoinflammatory disease. Tr. 65-66. According to Dr. McCabe, when a person with a genetic susceptibility encounters an environmental trigger, the person's innate immune system falls out of balance. The result of this imbalance, for some people, is sJIA. Tr. 66-69, 92-93.

Dr. McCabe testified about the Bradford Hill criteria for causation.<sup>27</sup> In Dr. McCabe's view, several of these criteria supported finding that Gardasil can cause sJIA. Supporting criteria include the temporal sequence, the dose-response relationship, and biological plausibility. Tr. 97-99. Another factor, experimental evidence, was the springboard into a lengthy discussion about how human beings respond to a vaccine against some types of human papillomavirus.

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<sup>25</sup> This section of the decision and the section on Dr. Rose's testimony summarize pertinent portions of their testimony without necessarily discussing each page of the transcript. However, the entire transcript has been reviewed.

<sup>26</sup> If Dr. McCabe had disagreed with the diagnosis from Vanessa's treating doctors, his testimony about an alternative diagnosis might have been problematic because Dr. McCabe is not a medical doctor.

<sup>27</sup> After the hearing, Ms. Koehn filed the article in which the Bradford Hill criteria appear. Exhibit 48 (Sir Austin Bradford Hill, The Environment and Disease: Association or Causation?, 7 Proc. of the Royal Society of Medicine 295 (1965)).

Dr. McCabe spoke extensively about a 2005 article written by Dr. Pinto and colleagues. Tr. 100-04; see Exhibit 26. Dr. McCabe interpreted this study as showing that a vaccine against a particular strand of human papillomavirus caused the production of various pro-inflammatory cytokines. Tr. 103-04, 110-11.

The discussion about the 2005 Pinto article flowed into testimony about a more recent article in which Dr. Pinto appears as the senior author. Exhibit 28 (García-Piñeres). Again, the authors used a vaccine against one strand, type 16, of the human papillomavirus. This study also showed that various cytokines increased after the administration of a vaccine against human papillomavirus. Tr. 117-19.

Dr. McCabe summarized his opinion why Gardasil can cause sJIA. His opinion is based, in part, upon “the scientific and medical literature that implicates proinflammatory cytokines and inflammatory responses and innate immunity in the pathogenesis of systemic juvenile arthritis.” His opinion is also based, in part, upon the “scientific and medical literature that demonstrates that HPV vaccine is a strong and potent immunogen that stimulates the production of these same proinflammatory cytokines.” Tr. 123.

At this point, Dr. McCabe moved to explain why Gardasil caused Vanessa’s sJIA. Dr. McCabe saw evidence that Vanessa was generating pro-inflammatory cytokines in her clinical presentation, including a fever, rash and joint pain. Tr. 123. Dr. McCabe also maintained that when Vanessa was given medications intended to reduce pro-inflammatory cytokines, such as Enbrel, methotrexate, and prednisone, her disease improved. Tr. 124-25. Dr. McCabe also suggested that Vanessa’s sJIA worsened after she received the third dose of Gardasil on August 19, 2008. Dr. McCabe, however, cautioned that when Vanessa received this dose, she was on anti-inflammatory therapies. Thus, whether the third dose of Gardasil caused Vanessa’s sJIA to flare was “not necessarily clear.” Tr. 126.

The next topic of Dr. McCabe’s direct testimony was the medically appropriate interval between vaccination and the onset of symptoms. Dr. McCabe stated that any adverse consequence of the vaccination is likely to arise in “the time period that measurable changes in the immune response are known to be elicited by the vaccine.” Tr. 128. Relying upon various studies, Dr. McCabe stated, by reference, that the medically appropriate immune response range would extend to approximately seven months after the vaccination. Tr. 127-29; see also exhibit 25 at S13.

Dr. McCabe's final topic was to address a study by Chun Chao and others. Exhibit 34. Despite involving approximately 189,000 people, Dr. McCabe asserted that the size of the study was not sufficiently large to detect any increase in the number of cases involving sJIA because sJIA is a rare disease. Tr. 133-34. Therefore, Dr. McCabe agrees with Berent Prakken, the author of another article on juvenile idiopathic arthritis, who recommended that "much larger studies . . . will be needed to define the role of environmental triggers in JIA." Tr. 136 (quoting exhibit 12 at 4).

For all these reasons, Dr. McCabe concluded, to a reasonable degree of scientific certainty, that the first two doses of the Gardasil vaccine caused Vanessa to develop sJIA.<sup>28</sup> Tr. 136-38.

On cross-examination, Dr. McCabe acknowledged that the Prakken article states "Infections and vaccinations have been suggested as two candidate triggers, but neither has been confirmed because of the scarcity of proper control perspective studies." Tr. 140 (quoting exhibit 12 at 2141). The studies that looked for a connection between vaccination and juvenile idiopathic arthritis concerned the meningococcal vaccine and the MMR vaccine. Id.

Dr. McCabe stated that clinicians and basic researchers have been investigating the causes of sJIA for a long time. But, they have not identified the cause because it is a "multifactorial disease." Tr. 143-44. In this regard, Dr. McCabe stated that there is "no epidemiology that's meaningful enough to inform us" as to whether the HPV vaccine causes sJIA. Tr. 141-42. Dr. McCabe also acknowledged that he had not located any case reports describing an association between HPV vaccine and sJIA. Id. Dr. McCabe is not aware of anyone conducting a case control study of whether HPV vaccine causes sJIA. Tr. 147.

Counsel for the Secretary probed Dr. McCabe's reliance on medical articles. For example, counsel noted the 2005 Pinto article does not mention any type of arthritis, including sJIA, does not propose any theory to connect an HPV vaccine to sJIA, and does not report that anyone who received the vaccination developed any

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<sup>28</sup> Ms. Koehn's counsel asked Dr. McCabe if he held his opinions "to a reasonable degree of scientific certainty," and Dr. McCabe answered affirmatively. Tr. 137. Dr. McCabe could have testified if he held his opinions only to a reasonable degree of scientific probability.

symptoms. Tr. 147-48. For the last point, Dr. McCabe pointed out that because the study did not report any consequence, it is impossible to know whether any test subjects experienced any adverse events. Tr. 148-49. Government counsel and Dr. McCabe reviewed similar limitations to other articles, including the García-Piñares article. Tr. 149-50.

In regard to the Chao article, Dr. McCabe stated that the researchers considered juvenile rheumatoid arthritis. Tr. 155 (citing exhibit 34 (Chao) at 197). The abstract of this article states “No autoimmune safety signal was found in women vaccinated with HPV-4.”<sup>29</sup> Tr. 156 (quoting exhibit 34 at 193).

In Vanessa’s medical history, none of her treating doctors expressed any opinion as to whether the HPV vaccine caused her to develop sJIA. Dr. McCabe did not see any indication that Vanessa’s treating doctors were concerned about giving her the third dose of Gardasil after she had developed sJIA. Tr. 156-57. Dr. McCabe recognized that it appears that shortly before the third dose of Gardasil, Vanessa had stopped taking prednisone but was improving on Enbrel. Tr. 158 (citing exhibit 5 at 45-46).

Dr. McCabe stated that hypothetically, if Vanessa had not received Gardasil and still developed sJIA, then he would not know what caused her to develop the disease. Tr. 160. His opinion that Gardasil caused Vanessa to develop sJIA is based, in part, upon the timing and also upon the immunobiology of what is known about sJIA. Tr. 161.

Dr. McCabe also answered questions the undersigned asked. Dr. McCabe stated that after Ms. Koehn’s counsel first contacted him, there was a hypothesis that Gardasil caused Vanessa’s sJIA. He investigated whether “there was a tenable scientific argument” by conducting a scientific undertaking. He learned about sJIA. Tr. 164. He also looked for data to support the proposition that Gardasil causes an increase in pro-inflammatory cytokines. He also drew upon his experience and background. Tr. 164-65.

Dr. McCabe testified that the limited number of cytokines does not detract from his opinion that Gardasil causes a production of pro-inflammatory cytokines and these cytokines caused Vanessa’s sJIA. He stated that although a tool box

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<sup>29</sup> Gardasil is the vaccine against four strands of the human papillomavirus.

may have many tools, it is likely that a hammer was used to pound a nail. Tr. 172-73.

Dr. McCabe recognized that some of the Bradford Hill criteria do not support a finding of causation. For example, the “strength of association” is not supportive. In addition, the criteria of “analogy” would either be not supportive or not relevant. The studies involving juvenile idiopathic arthritis and either the MMR vaccine or the meningococcal vaccine do not link the disease with the vaccine. If the MMR vaccine and/or the meningococcal vaccine were analogous to Gardasil, then those studies would counter the hypothesis that Gardasil can cause sJIA. However, Dr. McCabe suggested that the MMR vaccine and the meningococcal vaccine differed from Gardasil. See Tr. 179-83.

Additionally, Dr. McCabe agreed that Gardasil is not the only cause of sJIA. This fact is easily recognized because sJIA existed before Gardasil. Tr. 173-74, 190-91.

In regard to Vanessa’s case specifically, the undersigned asked how Dr. McCabe could distinguish a case of sJIA caused by Gardasil from a case of sJIA caused by something else. Dr. McCabe’s response was relatively weak. Although not phrased in these terms, he essentially stated that among all the things to which Vanessa was exposed, the only possible cause for sJIA was Gardasil. See Tr. 191-94.

After a short redirect examination, Dr. McCabe confirmed that his opinion remained unchanged. He stated that Gardasil caused Vanessa’s sJIA. Tr. 195-97.

## **2. Respondent’s Expert, Carlos Rose, M.D.**

### **a) Qualifications**

Dr. Rose graduated from Argentina’s University of Buenos Aires in 1977. He passed his boards for rheumatology while still in Argentina in 1983. By 1987, Dr. Rose was living in the United States, participating in an internship in pediatrics at the Medical Center of Delaware. He had successive fellowships in pediatric rheumatology, first at the Children’s Hospital of Philadelphia and then at Alfred I. duPont Institute in Delaware. He has held a board certification in pediatrics with a specialty in rheumatology since 1998. Dr. Rose estimated that there are 216 pediatric rheumatologists in the United States. Exhibit B (curriculum vitae) at 1-5; Tr. 199-200.

He has worked as a staff physician in pediatric rheumatology at the Alfred I. duPont Institute since 1991. In 1994, he became chief of the rheumatology division. He has taught pediatrics at the Jefferson Medical College of Thomas Jefferson University since 1991, and he became a full professor at that school in 2002. Exhibit B at 6-7.

He has served on international committees and lectured to audiences in foreign countries. Dr. Rose has written more than 70 peer-reviewed articles. He also has written more than 25 book chapters or monographs. Some publications relate to juvenile idiopathic arthritis, but not specifically to sJIA. Exhibit B at 13-20; Tr. 202-03.

As part of voir dire, Ms. Koehn's counsel elicited the following points about Dr. Rose's qualifications. He is not an immunologist and he has not researched the role of pro-inflammatory cytokines in causing sJIA. He has not done any research on any human papillomavirus vaccine, including Gardasil. Tr. 204.

Dr. Rose stated that he has worked for the Department of Health and Human Services in the Vaccine Program for 21 years. Over that span, Dr. Rose estimated that he has reviewed approximately 60 cases. He recommended compensation in one case. Tr. 205-07.

The Secretary offered Dr. Rose as an expert in the field of pediatric rheumatology. After Ms. Koehn did not object, he was recognized in that field. Tr. 207.

## **b) Reports**

In Dr. Rose's first report, he begins with a summary of Vanessa's medical history. Dr. Rose agrees that she suffers from sJIA. Exhibit A at 1.

He states that sJIA is an "auto-inflammatory disease[] likely associated with dis-regulation [sic] of cytokine networks likely IL-1 and IL-6 networks rather than the adaptive immune system." For this particular form of arthritis, Dr. Rose states that he is not familiar with any infections being associated with sJIA, although some infections have been associated with "transient self-limiting arthritis." In regard to the human papillomavirus, Dr. Rose states that that organism does not produce any arthritis and "no syndrome even remotely reminiscent of sJIA is seen in association with the infection." Id. at 2.

Dr. Rose rejects the idea that HPV vaccine can cause sJIA. Relying on a study that integrated many clinical trials, Dr. Rose states there was “no statistically significant difference in the event rates between vaccine and control groups.” Id. at 3, 8 (citing exhibit E (Verstraeten)). Dr. Rose also reviewed the literature that Dr. McCabe cited.

Dr. Rose’s first report concludes that “more likely than not Vanessa’s disease emerged as the result of chance and it was not causally related to the immunizations she received.” Id. at 7. Dr. Rose’s supplemental report makes a similar point: “the temporal association between vaccine and disease onset is coincidental.” Exhibit F at 1.

The supplemental report presents Dr. Rose’s opinion regarding Dr. McCabe’s cytokine theory. Dr. Rose asserts that “[t]he cytokine response is complex and cytokines that in certain circumstances are pro-inflammatory, in others are anti-inflammatory, depending on the combination of signals, the tissue in question and even perhaps the age of the individual.” He maintains that “[t]he fact that similar cytokines are found in serum of sJIA patients and in vaccine response is more a reflection of the somewhat limited and stereotypical inflammatory response repertoire in mammals than a suggestion for a link [between] vaccine [and] sJIA.” Id.

### **c) Testimony**

After Dr. Rose was accepted as an expert in pediatric rheumatology, he summarized the material that he reviewed in this case. He offered his opinion that the Gardasil vaccinations were not related to Vanessa’s development of sJIA. Tr. 208.

Dr. Rose agreed that Vanessa suffers from sJIA. sJIA, as set forth above, is not an autoimmune condition. It is an autoinflammatory condition. Dr. Rose explained that the treatment for sJIA is different medications, including corticosteroids (methotrexate). The purpose of some drugs is to inhibit cytokines such as interleukin 1, interleukin 6, and TNF. The way Vanessa’s doctors treated her was typical. Tr. 210-14.

Dr. Rose elaborated on cytokines and sJIA. He stated that interleukin 6 may be a cause of sJIA. Even if it is not a cause, interleukin 6 influences the course of the disease. For example, peaks in interleukin 6 preceding a rise in temperature

and a hectic fever are a defining characteristic of sJIA. Interleukin 1 has also been linked causally to arthritis. Dr. Rose stated that his experience as a clinician who has seen some (but not all) patients with sJIA improve after taking drugs that control interleukin 1 and interleukin 6 informs his belief that these cytokines play a role in the disease. Tr. 215-17.

Dr. Rose disputed the relevance of Dr. McCabe's citation to the Prakken (exhibit 12), Mellins (exhibit 13), and Rongahy (exhibit 15) articles. According to Dr. Rose, although these articles mention that infections could cause juvenile idiopathic arthritis, the articles were merely generating hypotheses that could be tested. To Dr. Rose, the articles did not report any evidence supporting Dr. McCabe's theory. See Tr. 217-18. According to Dr. Rose, pediatric rheumatologists are not discussing whether an HPV vaccine can cause sJIA. Instead, pediatric rheumatologists are discussing how safe the vaccines are for patients with sJIA. Tr. 219.

Dr. Rose testified that one way to look at the safety of vaccines is to give vaccines to people who have a disease and to see what happens. For juvenile idiopathic arthritis, there were studies involving the MMR vaccine and the meningococcal vaccine. Those studies showed that the MMR vaccine and the meningococcal vaccine did not affect people with juvenile idiopathic arthritis adversely. Tr. 221-23.

Dr. Rose is not aware of any epidemiological data connecting the HPV vaccine and sJIA. He also has not seen any case reports on this topic. Tr. 220.

Dr. Rose discussed some of the articles on which Dr. McCabe relied. For the Pinto article (exhibit 26), Dr. Rose examined whether cytokines remained elevated. Constancy in elevation was important to Dr. Rose because, as a clinician, he sees patients with a pattern of continually elevated cytokines. When Dr. Rose stops medications that inhibit the production of cytokines, the patients flare. But, when Dr. Rose looked at the data presented in the Pinto article, he did not see much difference in the amount of cytokines produced at zero months, two months, and seven months. To Dr. Rose, the Pinto data is "very suggestive that the response that this vaccine elicited in these normal people has not been sustained," and thus the vaccine-elicited cytokine response differs from the sustained pattern of "upregulation" he sees in his patients with sJIA. Tr. 223-26.

According to Dr. Rose, the García-Piñares article from 2007 (exhibit 28) in which Dr. Pinto appears as the senior author makes the same point. These

experiments showed that a vaccine can stimulate the production of cytokines when administered. But, in Dr. Rose's view, these experiments do not show how a single incidence of cytokine production can cause a disease. See Tr. 227-28.

Dr. Rose also discussed the Verstraeten (exhibit E) article, which he cited in his expert report. Exhibit A at 3, 8. Dr. Rose stated that "this is the closest that we can get to an epidemiologic study. This is a study of about 60,000 individuals." Tr. 232. Dr. Rose stated that if the vaccine were "a significant trigger[,] I would expect to see one or two cases of sJIA in the vaccinees." Id. However, Verstraeten and his colleagues found "no evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04 compared with controls." Exhibit E at 6633.

In regard to Vanessa, Dr. Rose said that he did not see any evidence that her treating doctors believed that the HPV vaccination caused her sJIA. Dr. Rose said that according to the standard of practice, even after Vanessa was diagnosed as having sJIA following the second dose of Gardasil, she still should receive the third dose. Dr. Rose said that he recommends that his patients with sJIA receive the HPV vaccine. For Vanessa, although she had a rash and increased joint pain after the third dose of Gardasil, Dr. Rose stated that this flare was due to the discontinuation of corticosteroids. Dr. Rose said that this pattern of stopping the medication and worsening of the condition happened earlier. Tr. 232-34.

On cross-examination, Ms. Koehn's counsel elicited the following testimony from Dr. Rose. The Verstraeten article did not involve Gardasil and involved a vaccine that had a different adjuvant from the adjuvant in Gardasil. There was some question about whether the Verstraeten article was looking for cases of sJIA. Tr. 240-44.

Dr. Rose stated that the incidence (new cases per year) of sJIA is between 0.3 and 0.8 per 100,000 people. Tr. 244. This fact was the starting point for a discussion between counsel and Dr. Rose about how large a population sample would be needed to power an epidemiological study involving sJIA. This colloquy did not provide especially helpful testimony in that Dr. Rose said, "I really need a calculator or somebody to help me to really calculate it. . . . So maybe you need 100,000. I don't really know the answer. . . . At least you need 100,000." Tr. 245-46.

Dr. Rose stated that in the Chao article, the researchers were looking for cases of "juvenile rheumatoid arthritis." Tr. 248 (discussing exhibit 34 at 194).

Dr. Rose maintained that, although the article was published in 2011, the researchers were using an out-of-date term. Dr. Rose believed that the term “juvenile rheumatoid arthritis” would capture cases of sJIA. Tr. 248-52.

Ms. Koehn’s counsel also inquired about the Gardasil package insert, which Dr. Rose had cited in his expert report. Ms. Koehn’s counsel raised two issues. First, whether the phase 3 or phase 4 clinical trials would have identified cases of sJIA that followed the administration of Gardasil. Dr. Rose said that if there were any cases, then they would have been reported. Second, whether the number of subjects in the clinical trials would have detected any changes in the incidence of sJIA. Dr. Rose stated that although there were about 10,000 vaccinees and a similar number of controls, if the vaccine caused sJIA, there would be some cases reported. Tr. 252-60.

#### **d) Post-Hearing Report**

Due to questions about the scope of the Chao research that arose during the hearing, Dr. Rose was permitted to file a brief supplemental report. It explained the process of identifying diseases in women who had received Gardasil. Exhibit F.

### **III. Standards for Adjudication**

To receive compensation under the Program, Ms. Koehn must prove either: (1) that Vanessa suffered a “Table Injury”—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that Vanessa suffered an injury that was actually caused by Gardasil. See 42 U.S.C. §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec’y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Here, Ms. Koehn is not claiming an injury listed on the Vaccine Table. Therefore, she must prove causation-in-fact.

When a petitioner proceeds on a causation-in-fact theory, a petitioner must establish three elements. The petitioner’s

burden is to show by preponderant evidence that the vaccination brought about [the] 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, 418 F.3d at 1278.

In this passage, Althen indicates that petitioner's burden of proof is a preponderance of the evidence. Accord 42 U.S.C. § 300aa-13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

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 judgment that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (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). In this regard, “close calls regarding causation are resolved in favor of injured claimants.” Althen, 418 F.3d at 1280.

Ms. Koehn argues she has provided preponderant evidence to meet her burden under Althen to prove Vanessa's sJIA was caused in fact by her Gardasil vaccinations. An evaluation of each prong follows.

#### **IV. Prong One from Althen – Medical Theory**

The starting point for analysis is the theory proposed by the expert that “causally connect[s] the vaccination and the injury.” Althen, 418 F.2d at 1278. This element of petitioner's case is sometimes referred to as answering the “can it” question. Pafford v. Sec'y of Health & Human Servs., No. 01-165V, 2004 WL 1717359, at \*4, 9 (Fed. Cl. Spec. Mstr. July 16, 2004), mot. for review denied, 64 Fed. Cl. 19 (2005), aff'd, 451 F.3d 1352 (Fed. Cir. 2006).

To explain how Gardasil harmed Vanessa, Ms. Koehn presents a theory dependent upon relatively complex medical knowledge. Special masters have been instructed in how to evaluate this type of evidence. See section IV.A below. The evidence is analyzed in section IV.B.

## A. Considerations of Scientific and Medical Evidence

As Congress authorized, the judges of the Court of Federal Claims have collectively issued the Vaccine Rules. 42 U.S.C. § 300aa-12(d)(2). The Vaccine Rules, in turn, provide that the special master “must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties.” Vaccine Rule 8(b)(1); see Cedillo v. Sec’y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (stating “Vaccine Rule 8(b)(1) necessarily contemplates an inquiry into the soundness of scientific evidence to be considered by special masters”).

The reliability of expert testimony is a topic on which the Federal Circuit has guided special masters. The leading case is Terran v. Sec’y of Health & Human Servs., 195 F.3d 1302 (Fed. Cir. 1999). In Terran, the special master “examined” the expert’s opinion “in the light of the four guideposts enumerated in Daubert,” and “conclude[d] that petitioner’s theory of causation is not based on reliable scientific evidence.” Terran v. Sec’y of Health & Human Servs., No. 95-451V, 1998 WL 55290, at \*11 (Fed. Cl. Spec. Mstr. Jan. 23, 1998) (citing Daubert v. Merrell Dow Pharma., Inc., 509 U.S. 579 (1993)). When Ms. Terran’s appeal reached the Federal Circuit, she argued that “the Special Master improperly applied the Daubert factors to the expert’s testimony.” The Federal Circuit rejected this argument and indicated that the special master reasonably used “Daubert’s questions as a tool or framework for conducting the inquiry into the reliability of the evidence.” Terran, 195 F.3d at 1316.

After Terran, decisions from judges of the Court of Federal Claims have consistently cited to the Daubert criteria as useful in assessing an opinion that a vaccine can cause an injury. See, e.g., Snyder v. Sec’y of Health & Human Servs., 88 Fed. Cl. 706, 742-45 (2009); Cedillo v. Sec’y of Health & Human Servs., 89 Fed. Cl. 158, 181-82 (2009), aff’d, 617 F.3d at 1338; Bazan v. Sec’y of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) (“A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness’s testimony regarding causation.”), rev’d on other grounds, 539 F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec’y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec’y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

The reliability of the expert’s theory is not presumed. A “special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” Moberly, 592 F.3d at 1324 (citing Terran, 195 F.3d at 1316).

Furthermore, the reliability of an expert's theory affects the persuasiveness of the evidence. Special masters may "inquir[e] into the reliability of testimony from expert witnesses. Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." Moberly, 529 F.3d at 1325 (citing Terran, 195 F.3d at 1316).<sup>30</sup>

The mere proffer of a theory does not satisfy petitioners' burden on this prong. If the special master finds that the expert's theory is supported by only an "ipse dixit," then the special master may reject this opinion. Snyder, 88 Fed. Cl. at 745 n.66 (2009) (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)); see also Cedillo, 617 F.3d at 1339 (also quoting Joiner, 522 U.S. at 146).

To avoid presenting just an unadorned statement from an expert, petitioners typically present medical articles on which the expert relies. When the petitioner

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<sup>30</sup> In her post-hearing brief, Ms. Koehn consistently described Dr. McCabe's theory as "biologically plausible." Pet'r Br., filed Sept. 21, 2012, at 8, 12 (citing Doe 93 v. Sec'y of Health & Human Servs., 98 Fed. Cl. 553, 566-67 (2011)). The Secretary argued that Ms. Koehn was using the wrong standard. Resp't Br., filed Nov. 19, 2012, at 5 (citing Pet'r Br. at 8). Nevertheless, Ms. Koehn continued to assert that she has advanced a "biologically plausible theory of causation." Pet'r Reply Br., filed Dec. 4, 2012, at 4 (capitalization changed without notation).

As discussed in the text, Moberly establishes that the correct standard of proof in evaluating a petitioner's theory is the preponderance of the evidence. Moberly, 592 F.3d at 1322. Although Ms. Koehn is accurate in citing Doe 93 in support of a plausibility standard, another Court of Federal Claims opinion respectfully disagreed with Doe 93. Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 144 n.18 (2011). Rather than use a plausibility standard, Caves used a preponderance of the evidence standard. Id. at 132 (stating "each of [the Althen] requirements must be proven by a preponderance of the evidence"). When the Federal Circuit reviewed Caves, it affirmed without opinion pursuant to Federal Circuit Rule 36. 463 F. Appx. 932 (Fed. Cir. 2012). The Federal Circuit's Rule 36 adjudication indicates that "a judgment or decision has been entered without an error of law." Thus, the precedential authority supports the preponderance of the evidence standard.

presents medical articles, the special master may evaluate those articles.<sup>31</sup> Andreu, 569 F.3d at 1379-80 (“[T]he special master can consider [medical literature or epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.”) (citing Daubert, 509 U.S. at 593-97). The Secretary, too, may offer articles that contradict a petitioner’s theory. Stone v. Sec’y of Health & Human Servs., 676 F.3d 1373, 1379-80, reh’g en banc denied, 690 F.3d 1380 (Fed. Cir. 2012), cert. denied, --- S.Ct. ---, 2013 WL 328557 (2013); Bazan, 539 F.3d at 1353 (stating “[t]he government, like any defendant, 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 [sic].”).

In evaluating expert testimony and scientific literature, special masters should analyze scientific literature “not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act’s preponderant evidence standard.” Andreu, 569 F.3d at 1380. “In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence.” Broekelschen v. Sec’y of Health & Human Servs., 89 Fed. Cl. 336, 343 (2009), aff’d, 618 F.3d 1339 (Fed. Cir. 2010).

When an expert’s opinion is not supported, the special master may find petitioner’s proof was inadequate. Althen, 418 F.3d at 1278 (“A persuasive medical theory is demonstrated by ‘proof of a logical sequence of cause and effect’ . . . supported by ‘reputable medical or scientific explanation[,]’ i.e., ‘evidence in the form of scientific studies or expert medical testimony.’”) (quoting Grant v. Sec’y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992)); see also Shapiro v. Sec’y of Health & Human Servs., 105 Fed. Cl. 353, 360 n.5 (2012) (denying motion for review and stating “the Special Master merely required that the theories be reliable and meet the preponderance of the evidence standard. He found each of [petitioner’s expert’s] explanations lacking in this regard, based upon major gaps and flaws in those theories, and instead was persuaded by [respondent’s expert’s] contradicting testimony.”), aff’d mem., 2013 WL 1896173 (Fed. Cir. 2013).

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<sup>31</sup> The special master, however, may not require medical literature. Althen, 418 F.3d at 1280.

These standards will be used to determine whether Ms. Koehn has met her burden of proof for the first prong of Althen.

## **B. Evidence Related to Prong One of Althen**

### **1. Overview**

Dr. McCabe's theory includes two distinct propositions: first, the production of inflammatory cytokines can cause sJIA, and, second, Gardasil can cause inflammatory cytokines. See Pet'r Br., filed Sept. 21, 2012, at 8-12 (organizing petitioner's prong one evidence around these two points). As previously summarized, Dr. McCabe relied primarily upon articles authored by Prakken, Mellins, Ronaghy, and Pinto. Exhibits 12, 13, 15 and 26.

Dr. Rose questioned the reliability of using cytokines to link Gardasil and sJIA. The formulation that: (1) Gardasil can cause an increase in particular cytokines; (2) those cytokines can contribute to sJIA; and, therefore, (3) Gardasil can be a significant factor in causing sJIA is oversimplified. The generation of cytokines is "very ubiquitous and [is] almost a universal response." Tr. 279. Further, people produce a finite number of cytokines, with perhaps as many as 40 being identified so far. Tr. 290; see also Tr. 172 (Dr. McCabe stating he "accept[s] to a certain extent that there is a commonality in the immune effector functions"). Thus, to Dr. Rose, "similarities in cytokine patterns . . . do not mean much in terms of causality." Tr. 219.

Given this dispute between the experts, the special master's responsibility is "to assess the reliability of testimony, including expert testimony" Moberly, 592 F.3d at 1325. One accepted method for evaluating the persuasiveness of an expert's opinion is to conduct an analysis using Daubert. Id. at 1324, citing Terran 195 F.3d at 1316.

The Supreme Court listed several non-exclusive factors that trial courts may consider in evaluating an expert's opinion:

- (1) whether a theory or technique can be (and has been) tested;
- (2) whether the theory or technique has been subjected to peer review and publication;
- (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and,
- (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing Daubert, 509 U.S. at 592-95). These factors will be used here.

## **2. Whether a Theory or Technique can be (and has been) Tested**

One way to test the theory that Gardasil can cause sJIA is to administer Gardasil to people and see how many people develop the disease. These epidemiological studies are discussed separately below.

In lieu of that type of testing, scientists (including Dr. McCabe) look to criteria listed by Sir Austin Bradford Hill. See exhibit 48; see also Tr. 97 (testimony from Dr. McCabe about the Bradford Hill criteria). Two criteria that are potentially useful here are responses to other vaccines and animal models.

### **a) Other Vaccines**

Dr. McCabe recognized that one way of inquiring was to “study exacerbation in individuals who have already been diagnosed and have the disease.” Tr. 134. Dr. McCabe also stated that considering studies with other vaccines would be “a reasonable hypothesis . . . to consider with a few caveats.” Tr. 181. Exploring how vaccinations affect people with a disease can inform the assessment of whether the vaccinations cause the disease. Tr. 222; see also W.C. v. Sec’y of Health & Human Servs., No. 07-456V, 2011 WL 4537877, at \*14-15 (Fed. Cl. Spec. Mstr. Feb. 22, 2011) (considering three studies about flu vaccination given to people with multiple sclerosis), mot. for review denied in relevant part and granted in non-relevant part, 100 Fed. Cl. 440 (2011), aff’d 704 F.3d 1352 (Fed. Cir. 2013).

The record contains the results of two studies involving vaccines and juvenile idiopathic arthritis. In both studies, the people given the vaccine already suffered from juvenile idiopathic arthritis and the researchers were studying whether the patient’s disease worsened after the vaccination. See generally, exhibit 43 (Heijstek) and exhibit 47 (Zonneveld-Huijssoon). One study involved MMR vaccine. In a retrospective analysis of 207 patients with juvenile idiopathic arthritis (of which 17 had sJIA), the researchers found “no changes in disease activity, flare occurrence or medication use after the MMR vaccination.” Thus, the

researchers concluded that the “MMR vaccination appears to be safe in JIA.” Exhibit 43 (Heijstek) at 1386.<sup>32</sup> The other study used the meningococcal C vaccination. The total number of participants was 234, including 34 with sJIA. Exhibit 47 (Zonneveld-Huijssoon) at 641. The researchers “did not detect any worsening of disease activity within 6 months after MenC vaccination.” Id. at 644.

Analogizing between how other vaccines affect patients with juvenile idiopathic arthritis and how Gardasil affects patients with sJIA, Dr. Rose stated that “these two vaccines seem to have a wonderful record of safety in patients with JIA.” Tr. 222. Dr. Rose added, that all vaccines, except live viral vaccines, are recommended to those who have JIA. Id.

Dr. McCabe pointed out that Gardasil induces a stronger response from the immune system than the natural infection. Tr. 181-82. Dr. McCabe also did not know whether the MMR vaccine or the meningococcal C vaccination induced the same type of cytokines as Gardasil induces. Tr. 183. Thus, the analogy between, on the one hand, either MMR vaccine or the meningococcal vaccine, and, on the other hand, Gardasil, is not perfect.

To the extent that some differences can be overlooked, the Heijstek and Zonneveld-Huijssoon studies suggest that when researchers have explored whether vaccinations affect juvenile idiopathic arthritis, they have not found that the vaccine worsens the disease. Because they are studies, the Heijstek and Zonneveld-Huijssoon findings are entitled to more weight than speculative passages in other articles. For example, a group of researchers, including Dr. Zonneveld-Huijssoon, stated “in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares, hint at a possible relation of JIA disease activity and vaccinations or infections.” Exhibit 15 (Ronaghy) at 1. As the Secretary argued, this language (“hint”) is “equivocal.” Resp’t Br. at 6.

#### **b) Animal Models**

Another way to test whether a substance causes a disease is to substitute animals for people. If the animals develop the disease, then people might, too. See

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<sup>32</sup> Dr. Heijstek and colleagues added a caveat that the statistical power of their study was limited and recommended a prospective trial. Id.

Tr. 176 (Dr. McCabe’s testimony that if he had unlimited funding to study the causes of sJIA, he would “possibly look for some changes in animal models”).

Here, there are no animal models for sJIA. However, animal models do exist for a related disease, macrophage activation syndrome. Dr. McCabe and Dr. Rose agreed that macrophage activation syndrome is similar to, although not exactly the same as, sJIA. Tr. 76 (Dr. McCabe), 219 (Dr. Rose), 285 (Dr. Rose), 297-98 (Dr. McCabe); see also exhibit C (Textbook) at 241 (discussing macrophage activation syndrome within a chapter on sJIA). While Dr. Rose suggested that a worsening of symptoms after injecting MAS-afflicted mice with specific vaccines would give us clues about the effects of certain vaccines compared to others, Tr. 219, 285, there was no evidence showing that this experiment was conducted.<sup>33</sup>

Dr. Rose further indicated that, in his opinion, this experiment is unlikely to be conducted. Dr. Rose explained that researchers are pursuing hypotheses around sJIA that are more likely to produce advancements than the theory that Gardasil can cause sJIA. Tr. 220-22.

Overall, the evidence relating to testing does not assist Ms. Koehn. From her perspective, the most favorable interpretation is that this factor is neutral (neither supporting nor discounting) because the most on-point testing has not been done. Another interpretation is that this factor is against Ms. Koehn’s theory because the testing that has been done with other vaccines and sJIA has refuted a connection between those vaccines and sJIA.

### **3. Whether the Theory or Technique has been Subjected to Peer Review and Publication**

The theory that Gardasil can cause sJIA has not been subject to peer review or publication. Dr. McCabe’s attempt to combine two ideas— (1) that pro-inflammatory cytokines can cause sJIA and (2) that Gardasil can cause pro-inflammatory cytokines—appears to be unprecedented. As the Secretary points out, until Ms. Koehn’s case, there was not even one case report published in the

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<sup>33</sup> Neither party introduced any articles discussing the extent of experiments on animals with macrophage activation syndrome.

medical journals showing even a temporal sequence in which a Gardasil vaccination preceded sJIA. Resp't Br. at 9.

The peer-reviewed article on which Dr. McCabe most heavily relied was Pinto. Dr. McCabe saw Pinto as supporting his theory because Pinto demonstrates, in some circumstances, increased levels of cytokines are present seven months after vaccination. The specific part of the Pinto experiment on which Dr. McCabe relied was when blood from a vaccinated person was stimulated with the virus-like particle. See Tr. 104-12.

Dr. Rose opined that a different part of the experiment was more meaningful. He stated that for purposes of evaluating a possible connection between HPV vaccination and sJIA, the relevant portion is the media. To Dr. Rose, this part of the experiment showed how the cells “are before and after vaccination, how the cells behave when you leave them alone.” Tr. 224. When Dr. Rose analyzed the data regarding the media, he saw that “for almost no cytokine there’s a spontaneous release of cytokines that is different at time zero compared to time two and time seven.” Tr. 225. The researchers came to the same conclusion: “As shown in Fig. 1D, spontaneous secretion of cytokines in the absence of any stimuli (media control) did not show any significant increases following vaccination.” Exhibit 26 (Pinto) at 3560. In other words, each successive administration of HPV vaccine did not produce any increase in cytokines. Cytokine levels increased only when researchers reintroduced the agent against which the vaccine was designed to protect.

Dr. Rose was less interested in the data showing the production of cytokines after the blood cells were stimulated with more of the L1 virus-like particle. He stated: “[o]f course, when you stimulate with an antigen you get more” cytokines released. Tr. 265.

Despite contrary testimony from Dr. McCabe (see Tr. 293-96, 301-03), Dr. Rose’s focus on the media column is logical. The blood in the media encountered the L1 virus-like particle only in the context of the three doses of vaccination. This pattern resembles what happened to Vanessa in the sense that no medical record suggests that she was exposed to a living strand of the human papillomavirus. If Vanessa encountered the human papillomavirus after the vaccination, the Pinto article predicts that she would produce a robust immune response like the ones reported for 10 µg and 1.0 µg of the virus-like particle.

The Pinto experiment also undermined the cohesiveness of Dr. McCabe's theory, particularly in regard to timing both for onset of symptoms and duration of symptoms. To review, after human beings are exposed to an antigen, they produce cytokines immediately. Tr. 281-82 (Dr. Rose's testimony that "from stimulus to response is a question of hours"). But, in Dr. McCabe's theory, the onset of disease can occur as long as seven months after vaccination. Tr. 127-29 (citing exhibit 25 (Frazer) at S13).

Dr. McCabe explained that the delay could be due to the time needed to amplify the immune system's response. Tr. 300-01; see also Tr. 295. However, the media portion of the Pinto experiment contradicts Dr. McCabe's speculation about an amplification process. In Pinto, the cytokines increased only when the blood was restimulated. When the blood was left alone, the cytokine level stayed relatively constant. This lack of continued elevation in pro-inflammatory cytokines was inconsistent with how sJIA persists. In Dr. Rose's experience in treating people with sJIA, those patients constantly need to receive medications to prevent development of pro-inflammatory cytokines. When the medication stops, the person has a flare in her (or his) disease. Tr. 224. Dr. McCabe, who is not a medical doctor, agreed that "cytokine dysregulation in sJIA isn't a transient event." Tr. 305. But, when he was asked about why sJIA is a chronic disease, Dr. McCabe did not provide a persuasive explanation. Tr. 305.

Overall, the evidence relating to peer review and publication does not assist in finding that Dr. McCabe's theory is probable. The peer-reviewed articles about epidemiology are taken up separately.

#### **4. Whether There is a Known or Potential Rate of Error and Whether There are Standards for Controlling the Error**

No evidence was introduced on this topic. An error rate for Dr. McCabe's theory cannot be calculated. Thus, this factor does not constitute affirmative or negative evidence.

## **5. Whether the Theory or Technique Enjoys General Acceptance within a Relevant Scientific Community<sup>34</sup>**

Except for the portion of the Prakken article discussed above, Ms. Koehn has not presented any evidence that the relevant scientific community generally accepts the theory that Gardasil can cause sJIA. See Pet'r Reply Br. at 14-15. The Secretary has presented evidence (the opinion of Dr. Rose) that shows that the theory is not generally accepted.

Dr. Rose is the head of pediatric rheumatology at the Alfred I. DuPont Hospital for Children. Exhibit B (curriculum vitae); Tr. 200. He conducts research on juvenile rheumatoid arthritis, although not on sJIA. Tr. 202. He attends conferences held by associations of rheumatologists. Tr. 283-84. He serves as an editor for Clinical Rheumatology. Exhibit B at 9. Given this background, it seems likely that if rheumatologists were considering whether Gardasil can cause sJIA, then Dr. Rose would have heard some discussion about this theory. However, Dr. Rose testified that he did not recall hearing about this idea. Tr. 284.

Furthermore, Dr. Rose stated that the general practice among rheumatologists is to recommend vaccinations for their patients with sJIA. See Tr. 219, 222. This practice reflects a belief that the benefits from vaccination outweigh the potential harm from vaccination. Although, conceivably, at some future time, rheumatologists will generally accept the theory that Gardasil can cause sJIA, the evidence in this case is that they do not.

## **6. Additional Considerations**

In defining how district court judges should determine whether expert opinion is admissible, the Supreme Court has emphasized that the approach should be "flexible." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (citing Daubert, 509 U.S. at 594). Thus, the analysis of whether the theory that

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<sup>34</sup> Citing Capizzano, 440 F.3d at 1325, Ms. Koehn argues that a petitioner is not required to show a particular theory has general acceptance. Pet'r Br. at 15. It is correct that special masters may not require general acceptance. However, pursuant to Terran, special masters may consider whether a particular theory has general acceptance as one factor in the overall analysis. 195 F.3d at 1316.

Gardasil can cause sJIA may consider more than just the four factors explicitly listed in Daubert. Two other factors are the origins of the theory and epidemiological studies.

**a) Genesis of the Expert’s Theory**

One consideration is why the expert came up with the opinion. On remand from the Supreme Court, the Ninth Circuit stated:

One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist’s normal workplace is the lab or the field, not the courtroom or the lawyer’s office.

Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1317 (9th Cir. 1995).

Here, Dr. McCabe developed his theory for the purpose of litigation. From his initial consultation, he understood that petitioner was hypothesizing that Gardasil caused Vanessa’s sJIA. From that starting point, Dr. McCabe investigated whether “there was a tenable scientific argument” and produced his report accordingly. Tr. 164. This factor, although not decisive, weighs against Dr. McCabe’s theory.

**b) Epidemiological Studies**

The Federal Circuit has endorsed consideration of epidemiological studies as one factor in the special master’s analysis. See W.C. v. Sec’y of Health & Human Servs., 704 F.3d 1352, 1361 (Fed. Cir. 2013) (holding that the special master was not arbitrary in denying compensation and summarizing epidemiological studies cited by the special master); Lampe, 219 F.3d at 1365 (stating “[a]n epidemiological study may be probative medical evidence relevant to a causation determination”). The special master may not find against a petitioner solely because the petitioner did not introduce supporting epidemiology. Capizzano, 440 F.3d at 1325.

Ms. Koehn acknowledges that she has not presented any epidemiology. Pet'r Br. at 15. The Secretary, on the other hand, relies upon the results of two studies that looked for but did not find an increased incidence of disease after vaccines against human papillomavirus. Resp't Br. at 7-8 (citing exhibit 34 (Chao) and exhibit E (Verstraeten)).

Ms. Koehn's cross-examination of Dr. Rose brought out two weaknesses in this reliance on the Verstraeten article. First, as mentioned above, Gardasil is not the same as Cervarix. Tr. 240. Logically, it is possible that a component of Gardasil that is not in Cervarix could cause unintended side effects that would not be identified in studies about Cervarix. Second, the size of the Verstraeten study, despite including more than 60,000 people, is still not large enough to discover an increased risk of sJIA. This argument derives from the incidence of sJIA, which is approximately 0.3 to 0.8 per 100,000 people in the United States. Tr. 244-45; but see Tr. 133 (Dr. McCabe's testimony that the incidence of sJIA is between 2 and 20 cases per 100,000 people). Given the frequency with which new cases develop, Dr. Rose was reluctant to estimate the size of an adequately powered study, although he speculated the size might be 100,000 people. Tr. 245-46.

In addition to the Verstraeten study, the other epidemiological study was authored by Chun Chao. Ms. Koehn reasonably could not repeat the attacks used against the Verstraeten article in response to the Chao article. Unlike the population Verstraeten analyzed, the Chao study subjects received Gardasil. Compare exhibit E (Verstraeten) at 6631 with exhibit 34 (Chao) at 193 and Tr. at 132 (Dr. McCabe noting that HPV-4, referred to in the Chao study, is Gardasil). In addition, Chao looked at more than twice as many women. Compare exhibit 34 (Chao) at 193 (n = 189,629) with exhibit E (Verstraeten) at 6630 (n = 68,512). Instead, Ms. Koehn called into question the supposition that Chao researchers would have identified cases of sJIA. See Pet'r Reply Br. at 14.

Based on the population analyzed by Chao and her colleagues and the incidence of sJIA, the study appears to be robust. According to the results, however, "no cluster of disease onset in relation to vaccination timing, dose sequence or age was found for any autoimmune condition." Exhibit 34 at 193. In other words, "[n]o autoimmune safety signal was found in women vaccinated with HPV4." Id. While an epidemiological study cannot prove that Gardasil does not cause autoimmune diseases as an absolute proposition, the results suggest that Gardasil causes an autoimmune disease extremely rarely, if it causes an autoimmune disease at all.

Taken together, the Verstraeten and the Chao articles are an additional (but not decisive) reason for finding that Dr. McCabe's theory that a vaccine against human papillomavirus can cause sJIA to be unlikely. The same result would have occurred even if the epidemiological studies were not part of the record.

### C. Summary

The Supreme Court has recognized that a novel theory that is relatively unexamined by the relevant scientific community may not be as persuasive as a theory that has been thoroughly peer-reviewed. This is so because "submission to the scrutiny of the scientific community . . . increases the likelihood that substantive flaws in methodology will be detected." Daubert, 509 U.S. at 593-94. The Daubert Court added, however, that the lack of publication is a "relevant, though not dispositive, consideration in assessing . . . scientific validity." Id. at 594. Special masters, too, have recognized that a theory's novelty is not dispositive in determining its scientific validity. Cedillo v. Sec'y, Health & Human Servs., No. 98-916V, 2009 WL 331968, at \*111 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) ("At times novel theories can be persuasive."), mot. for review denied, 89 Fed. Cl. 158, aff'd, 617 F.3d 1328. Ultimately, however, it is petitioner's burden to support her theory with "sufficient supportive evidence to justify the adoption of a proffered new theory." Cedillo, 2009 WL 331968, at \*111.

With respect to the first prong of Althen, Ms. Koehn's burden is to establish that Gardasil can cause sJIA. Her proof does not need to be scientifically certain; preponderant evidence suffices.

Here, the evidence does not weigh in Ms. Koehn's favor. Dr. McCabe, a Ph.D. immunologist, has pieced together a theory that, although not entirely impossible, contains sufficient gaps to make it unpersuasive. See Joiner, 522 U.S. at 146 (affirming exclusion of an expert's report when the trial court "conclude[d] that there [was] simply too great an analytic gap between the data and the opinion proffered"). Consequently, Ms. Koehn has not met her burden of proof.

## V. Prong Three from Althen – Timing<sup>35</sup>

Petitioners are required to establish a “showing of a proximate temporal relationship between vaccination and injury.” Althen, 418 F.3d at 1278. The Federal Circuit has elaborated that the third prong of the Althen test requires “preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder’s etiology, it is medically acceptable to infer causation.” Bazan, 539 F.3d at 1352. “Under this test, petitioner [is] first required to establish the timeframe for which it is medically acceptable to infer causation, that is, the timeframe in which symptoms would be expected to arise if the [disease] was caused by the vaccination. Then, she [is] obliged to show that the onset of her [disease] occurred during this causation period.” Shapiro v. Sec’y of Health & Human Servs., 101 Fed. Cl. 532, 542 (2011), recons. denied after remand, 105 Fed. Cl. 353 (2012), aff’d mem., 2013 WL 1896173 (Fed. Cir. 2013).

These two aspects are separately considered, beginning with findings related to when Vanessa’s sJIA began. After the relevant time for Vanessa is established, the next section reviews whether her onset date falls within a medically acceptable timeframe.

### A. What happened to Vanessa

Vanessia received the first dose of Gardasil on February 18, 2008, and the second dose on April 18, 2008. Exhibit 2 at 3. The experts agree that Vanessa’s sJIA became manifest in late June 2008. See Tr. 129 (Dr. McCabe stating “the disease emerged manifest in June of 2008”); Exhibit A (Dr. Rose’s report) at 1.<sup>36</sup> As the Secretary points out, the interval between vaccination and onset is approximately four months (using the date of the first dose) and approximately two months (using the date of the second dose). See Resp’t Br. at 14.

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<sup>35</sup> Since the third prong of Althen ties directly to Dr. McCabe’s theory, this decision discusses the third prong now. The second prong of Althen is discussed in section VI.

<sup>36</sup> Facts supporting the onset include: On June 21, 2008, Vanessa reported she had a rash all over her body. Exhibit 3 at 8. While hospitalized, Vanessa was diagnosed with systemic onset juvenile arthritis. Exhibit 4 at 11-12.

For Ms. Koehn to prevail, she must establish that two months (or four months) falls within the medically acceptable timeframe. Bazan, 539 F.3d at 1352; Shapiro, 101 Fed. Cl. at 542.

## **B. Time Expected by Medical Science**

The Court of Federal Claims has recognized that petitioners' proof of the medically acceptable time for an injury to appear after vaccination depends upon the petitioners presenting, pursuant to Althen prong one, a "reputable theory as to how the vaccination could cause the injury." Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 443 (2013). This linkage makes sense. If medical science understands how an injury might occur, then there would be some basis for understanding when the injury would occur. Conversely, if there is little understanding about the cause of a disease, then it is difficult to say when the disease should begin.<sup>37</sup> See Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) ("[T]he 'etiology' of the disorder determines the appropriate temporal relationship."), aff'd without opinion, 475 Fed. Appx. 765 (Fed. Cir. 2012). Moreover, analyzing the medically appropriate time from prong three in terms of the medical theory from prong one is in accord with the observation that evidence from one prong may overlap with another prong. Capizzano, 440 F.3d at 1326.

To Dr. McCabe, the "expected interval between vaccination . . . and the onset of the autoinflammatory disease is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine." Tr. 128. As discussed above, people receiving Gardasil produce antibodies against the human papillomavirus within seven months. See exhibit 25 (Frazer) at S13. Therefore, Dr. McCabe implies that an appropriate timeframe in which an individual can first exhibit symptoms of sJIA caused by Gardasil extends to up to seven months. See Pet'r Reply Br. at 16 ("[I]t follows that the interval

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<sup>37</sup> Dr. Rose expressed this idea when he stated "two months is as good as two hours or as good as six months since we really don't know what's going on." Tr. 308.

during which sJIA could be said to have a temporal association with Gardasil is the same 3-dose time frame, or within 7 months.”).<sup>38</sup>

Dr. Rose questioned why a theory involving cytokines could produce an injury after a delay of several months. As discussed in reference to Althen prong one, Dr. Rose stated, and Dr. McCabe agreed, that the immune system produces cytokines very quickly after it encounters an antigen. Tr. 281-82 (Dr. Rose); Tr. at 295 (Dr. McCabe). Thus, Dr. Rose expected that if vaccine-triggered cytokines contributed to the pathogenesis of sJIA, then symptoms of sJIA would “start[] right away.” Tr. 282.

Dr. McCabe’s theory holds that cytokines that are produced in response to the vaccination could lead to sJIA. He acknowledged that sJIA has genetic factors, “meaning that certain susceptible members of the population likely exist and develop this disease with or without environmental triggers.” Tr. 76. He then added that cytokines, activated by the vaccine, act on multiple tissues causing fever and the release of acute phase reactive proteins. Tr. 77-80. In his PowerPoint, he also acknowledged increased vascular permeability and increased synovial inflammation in response to cytokine activation. Exhibit 38 at slide 5 (reproducing figure 1 from exhibit 13 (Mellins) at 419). When asked to explain how the vaccine-stimulated cytokines cause the disease, Dr. McCabe referred to these consequences. Tr. 299. He also expected that “cytokine-mediated interactions between cells of the adaptive immune system and the innate immune system . . . are somehow playing a role in the disease,” but more sophisticated information was lacking. Tr. 299-300.

The lack of specificity in Dr. McCabe’s theory creates a gap in Ms. Koehn’s case. The consequences of cytokine production that Dr. McCabe identifies, such as fever, are usually apparent very quickly. The body’s rapid cytokine response appears inconsistent with Dr. McCabe’s assertion that the onset of disease could take many months.

Dr. McCabe attempted to answer this conundrum by opining that the onset of sJIA could be delayed because “there’s an amplification process.” Tr. 301. However, Dr. McCabe did not explain persuasively what he meant by that term.

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<sup>38</sup> As discussed below, Dr. McCabe did not directly discuss the interval in Vanessa’s case, which is two months.

see also Tr. 295. And specifically, Dr. McCabe did not explain why the immune system's production of cytokines would be amplified for weeks and months without a stimulant being present.

In sum, the record does not support a finding that the medically appropriate interval for a cytokine-mediated theory would extend out to seven months as Dr. McCabe proposed. Seven months might be appropriate for a different theory.<sup>39</sup> And seven months might be appropriate for a cytokine-mediated theory if there were some reliable evidence about how the cytokines start a lengthy process. But, because cytokines exist for a short duration, a preponderance of evidence does not support the finding that seven months is an appropriate medical interval.

More important for Ms. Koehn's case is whether a preponderance of the evidence establishes that two months is a medically appropriate interval because Vanessa's sJIA symptoms were recognized approximately two months after the second dose of Gardasil. See section V.A above. There was no testimony from either Dr. McCabe or Dr. Rose saying that two months is medically appropriate. In the absence of evidence, it is difficult to find that Ms. Koehn has met her burden of proof. Even two months is probably too long an interval for a cytokine-driven reaction. See James v. Sec'y of Health & Human Servs., No. 09-284V, 2010 WL 4205699, at \*6 (Fed. Cl. Spec. Mstr. Sept. 30, 2010) (summarizing testimony of the petitioner's expert that a child's death 14 hours after vaccination was consistent with release of cytokines); Doe/11 v. Sec'y of Health & Human Servs., No. 99-212V, 2008 WL 4899356, at \*28-30 (Fed. Cl. Spec. Mstr. Oct. 29, 2008) (discussing whether a cytokine storm can arise in four hours), mot. for review denied, 87 Fed. Cl. 1 (2009), aff'd, 601 F.3d 1349 (Fed. Cir. 2010).<sup>40</sup>

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<sup>39</sup> For example, in other cases, petitioners have proposed that a vaccine caused an autoimmune response involving either antibodies or T-cells. Ms. Koehn has not proposed a theory involving antibodies or T-cells because neither appears to be involved in the pathogenesis of sJIA. See Exhibit C (Textbook) at 236.

<sup>40</sup> These cases are consulted because (a) petitioner did not introduce any evidence about whether two months is a medically appropriate time and (b) special masters may use their "accumulated expertise" in evaluating the cases. Lampe, 219 F.3d at 1362 (quoting Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993)).

Ultimately, a finding on Althen prong three is not needed. Even if Ms. Koehn had established that there was a proper temporal sequence, timing does not entitle her to compensation. Grant, 956 F.2d at 1148. She is also required to establish a persuasive medical theory. Althen, 418 F.3d at 1278. As explained above, she has not met the first element and the failure to meet this element means that she cannot be compensated. See Hibbard v. Sec’y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding special master did not err in resolving the case pursuant to prong two when respondent conceded that petitioner met prong three).

## **VI. Prong Two from Althen – Logical Sequence of Cause and Effect**

The remaining Althen prong is “a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” 418 F.3d at 1278. Given the finding that Ms. Koehn has not established a persuasive theory to explain how Gardasil can cause sJIA, as a matter of logic, she cannot show that Gardasil did cause her sJIA. See Caves, 100 Fed. Cl. at 145. Nevertheless, the evidence particularly relevant to this factor is discussed for the sake of completeness.<sup>41</sup>

### **A. Factors to Consider in regard to Prong Two from Althen**

While the first prong from Althen is sometimes shortened to “can it?,” the second prong can be summarized as asking “did it?” See Pafford, 2004 WL 1717359, at \*4-5, 9. Evidence relevant to this prong “tends to be evidence specific for the petitioner.” Viscontini v. Sec’y of Health & Human Servs., No. 98-619V, 2011 WL 5842577, at \*20 (Fed. Cl. Spec. Mstr. Oct. 21, 2011), mot. for review denied, 103 Fed. Cl. 600 (2012). This focus on the petitioner particularly reflects the separate inquiries into the question of general causation (Althen prong one) and question of specific causation (Althen prong two). Veryzer, 100 Fed. Cl. at 353.

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<sup>41</sup> As part of her argument regarding Althen prong two, the Secretary argues that the two (or four) month delay between vaccination and onset of symptoms makes the logical sequence of events questionable. See Resp’t Br. at 10. Because section V.B above discussed the timing issue, the analysis of Vanessa’s chronology is not repeated here.

According to the Federal Circuit, the petitioner might present preponderant evidence on this prong by submitting evidence from treating doctors and/or evidence demonstrating challenge / rechallenge. Capizzano, 440 F.3d at 1325-26. This type of evidence focuses on the overriding issue in this case—whether Gardasil was a substantial factor in causing Vanessa’s sJIA. See Shyface v. Sec’y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Although Ms. Koehn argued that Vanessa’s presentation was consistent with pro-inflammatory cytokines, see Pet’r Br. at 13-14 (citing Tr. 123-25), this showing merely establishes that Vanessa suffered from sJIA. It does not show that the pro-inflammatory cytokines resulted from Gardasil. To be entitled to compensation, Ms. Koehn must present additional evidence. See Moberly, 592 F.3d at 1323 (holding that an appropriate temporal onset and “a simplistic elimination of other potential causes of the injury” does not meet petitioner’s burden) (quoting Althen, 418 F.3d at 1278).

## **B. Evidence Related to Prong Two from Althen**

### **1. Statements of Treating Doctors**

To demonstrate the “logical sequence of cause and effect,” the Federal Circuit has identified statements of treating doctors as probative evidence. Capizzano, 440 F.3d at 1326. Their views, however, are not necessarily “sacrosanct.” Snyder, 88 Fed. Cl. at 745 n.67.

Here, Ms. Koehn acknowledges that “Vanessia’s treating physicians did not express any opinion as to whether Gardasil was a cause of her development of sJIA.” Pet’r Br. at 14 (citing Tr. 157). Although this lack of connection from a treating doctor tends to make her claim less likely, Ms. Koehn points to a statement from one of Vanessa’s rheumatologists, Dr. Hoftman.

Dr. Hoftman worked within the University of California at Los Angeles (UCLA) Health System. Exhibit 5 at 28. Vanessa had been seen at UCLA since July 2008. Exhibit 3 at 11; exhibit 5 at 51. Dr. Hoftman saw her on January 12, 2011, as part of a periodic follow up. Exhibit 5 at 28. In the context of presenting a plan until Vanessa’s next appointment in three months, Dr. Hoftman wrote “Pt mother refused flu vaccine this year. Discussed [with] mom importance of this vaccine, risk < benefit. Mom hesitant b/c Gardasil. [Discussed with] mom – no

data but all vaccines and infections can trigger autoimmune response.” Exhibit 5 at 28.<sup>42</sup>

Dr. Hoftman does not express any agreement with Ms. Koehn’s concern about Gardasil. Dr. Hoftman actually appears to have recommended that Vanessa receive the flu vaccination and Vanessa would have been vaccinated against the flu at the January 12, 2011 appointment except that Ms. Koehn “refused flu vaccine this year.” In other years after Vanessa was diagnosed with sJIA, doctors had recommended, and Ms. Koehn had accepted their recommendation, that Vanessa receive a flu vaccination. See exhibit 5 at 32, 44, 60.

## 2. Challenge / Rechallenge

The advice to receive a flu vaccination is not necessarily inconsistent with a theory that Gardasil caused Vanessa’s sJIA because the flu vaccine is not the same as Gardasil. The more relevant inquiry is whether the doctors recommended an additional dose of Gardasil.

When patients encounter a putative causative agent a second time, they are considered to be facing a “rechallenge.” See Capizzano, 440 F.3d at 1322 (stating “[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”). The challenge-rechallenge paradigm is relevant to determining whether petitioners have demonstrated a “logical sequence of cause and effect.” Capizzano, 440 F.3d at 1326.

When the vaccinee’s medical history supports challenge-rechallenge, special masters have accepted this evidence as persuasive. Freeman v. Sec’y of Health & Human Servs., No. 04-1528V, 2009 WL 5103594, at \*12 (Fed. Cl. Spec. Mstr. Dec. 9, 2012); Hall v. Sec’y of Health & Human Servs., No. 02-1052B, 2007 WL 312084, at \*7 (Fed. Cl. Spec. Mstr. Oct. 4, 2007). On the other hand, petitioners have sometimes fallen short of demonstrating that their case truly fits the

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<sup>42</sup> To the extent that Dr. Hoftman expressed an opinion that “all vaccines . . . can trigger [an] autoimmune response,” Dr. Hoftman’s statement provides a modicum of support for Ms. Koehn’s prong one argument. It does not weigh very heavily in that regard because, as Dr. Hoftman states in that same sentence, there is “no data” for the proposition.

challenge-rechallenge model. Doe 70 v. Sec’y of Health & Human Servs., 95 Fed. Cl. 598, 608 (2010) (denying motion for review when the special master did not arbitrarily find that “the facts of petitioner’s case did not fit the challenge-rechallenge model”), aff’d sub nom., Rickett v. Sec’y of Health & Human Servs., 468 Fed. Appx. 952 (Fed. Cir. 2011); Locane v. Sec’y of Health & Human Servs., No. 99-589V, 2011 WL 3855486, at \*11 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), mot. for review denied, 99 Fed. Cl. 715, 732 (2011), aff’d, 685 F.3d 1375 (Fed. Cir. 2012).

Here, the parties draw different conclusions from how Vanessa fared after her third vaccination. The relevant chronology shows:

Date	Event	Citation
7/1/08	Dr. Scott diagnoses Vanessa with probable sJIA while she was hospitalized	Exhibit 4 at 11-12.
7/2/08	Dr. Regala, Vanessa’s pediatrician, refers Vanessa to UCLA / Dr. McCurdy	Exhibit 3 at 11.
7/8/08	Vanessa’s first appointment with Dr. McCurdy. The history notes that Vanessa had received two doses of the HPV vaccine. Dr. McCurdy continued the prescriptions for prednisone, methotrexate, Enbrel.	Exhibit 5 at 51-55.
8/19/08	Dr. Regala administers the third dose of Gardasil	Exhibit 3 at 6; <u>see also</u> exhibit 3 at 3-4.
8/25/08	During physical therapy, Vanessa had rash, chills, and joint pain.	Exhibit 8 at 48-50.
9/3/08	Vanessa returns to Dr. McCurdy. Her current medication was Enbrel. By history, Vanessa had “some improvement [with] Enbrel,” although she had “swollen knees [and] ankles.” Also, by history, after Vanessa “stop[ped] prednisone, [her] rash returned.” The doctor’s plan included continuing Enbrel and starting methotrexate. The doctor also ordered laboratory tests and if there were an increase in “inflammatory markers[,] may need prednisone.”	Exhibit 5 at 45-46.

Relying upon Dr. Rose’s testimony, the Secretary interprets this sequence as contrary to the challenge-rechallenge paradigm. According to the Secretary, “if the

HPV vaccine caused or substantially contributed to Vanessa's sJIA, then it would seem logical that a third dose of it on August 19, 2008 would have significantly exacerbated her symptoms."<sup>43</sup> The Secretary argues that the third dose of Gardasil did not make Vanessa worse because the rash was associated with stopping prednisone, not with the administration of the vaccine. Resp't Br. at 12.

Dr. McCabe's response is to emphasize a medication that Vanessa was taking—Enbrel. When Vanessa received the third dose of Gardasil, she was also taking an “anti-inflammatory therapy.” Tr. 126. Enbrel is a confounding factor. As Dr. McCabe explained: “If there were no changes, part of that would be I would suspect or wonder and consider whether well, the reason that there's no change is because at the same time that a stimulus is given an inhibitor is present.” Tr. 126.

In this context, Dr. McCabe stated that trying to determine whether the third dose of Gardasil made Vanessa worse is “difficult to say” because there are “[t]oo many variables.” Tr. 127. Any worsening could have been due to her stopping prednisone. Her continued use of Enbrel could have prevented any worsening that Gardasil would have caused absent the use of Enbrel.<sup>44</sup> In addition, there is the normal waxing and waning of sJIA.

The many confounding factors make reliance on Vanessa's experience after the third dose of Gardasil difficult in either respect. While it cannot be said that the Secretary has proven the absence of rechallenge, Ms. Koehn has not met her burden of proving that Vanessa's case constitutes an example of rechallenge.<sup>45</sup>

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<sup>43</sup> Dr. McCabe indicated that on an abstract level, this logic is an appropriate way to explore a cause and effect relationship. Tr. 125-26.

<sup>44</sup> Enbrel appears to help Vanessa cope with her disease. See exhibit 8 at 43 (noting, on February 25, 2009, that her hand hurt after she missed one dose of Enbrel).

<sup>45</sup> In its most recent report addressing whether vaccines cause injuries, the Institute of Medicine discussed the value of the rechallenge paradigm.

It is possible that one or more of the ‘challenges’ in an individual case patient reporting is related to coincidental exposure; thus, the committee looked for other information. . . . The value for the

(. . . continued)

### 3. Relative Qualifications of Experts<sup>46</sup>

In weighing the persuasiveness of opinion testimony, special masters may consider the relative expertise of the witness. Locane v. Sec’y of Health & Human Servs., 685 F.3d at 1380 (stating “[t]he Special Master found Dr. Warner’s testimony more persuasive than Dr. Bellanti’s because of their different backgrounds and specialties and because the medical literature supports Dr. Warner’s theory. . . . We find nothing arbitrary or capricious.”); Stone, 676 F.3d at 1382 (noting “[t]he special master found the respondent’s experts’ testimony on that issue to be more reliable than Dr. Kinsbourne’s in view of their more extensive and more recent experience”).

Dr. McCabe is not a medical doctor. Tr. 33. While Dr. McCabe’s lack of training and experience as a medical doctor could decrease the value of his opinion for any of the Althen prongs, see Resp’t Br. at 4-5 (discussing Dr. McCabe’s

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committee of rechallenge cases is much greater for monophasic conditions (events that typically happen only once, e.g., vasculitis) than for relapsing-remitting conditions, such as multiple sclerosis or rheumatoid arthritis.

Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality (Kathleen Stratton et al., eds. 2012). Although reports from the Institute of Medicine have informed decisions of special masters, see, e.g., Terran, 1998 WL 55290, at \*10-12, mot. for review denied, 41 Fed. Cl. 330, 337 (1998), aff’d 195 F.3d 1302 (Fed. Cir. 1999), the decision in Ms. Koehn’s case does not depend upon the views of the Institute of Medicine.

<sup>46</sup> In addition to the relative qualifications of the experts, both sides suggest that the other side’s expert may be biased. Neither of these arguments found their targets because both Dr. McCabe and Dr. Rose appeared to offer sincerely held opinions.

Nevertheless, Dr. McCabe derives more than 95 percent of his income from participating in litigation. Tr. 34. In Ms. Koehn’s words, his “professional activities revolve in large measure around participation in litigation.” Pet’r Reply Br. at 3. This concentration leaves Dr. McCabe open to a challenge that he is simply a professional witness.

credentials and background), the Secretary makes a particular argument for prong two. The Secretary contends that he “is not qualified to independently provide medical testimony and evidence on this issue.”<sup>47</sup> Resp’t Br. at 13.

Ms. Koehn replies that Dr. McCabe’s opinion should be given “substantial weight.” Pet’r Reply Br. at 3. Ms. Koehn notes that Dr. McCabe earned a Ph.D in microbiology and immunology. *Id.* While an assistant professor at Wayne State University, he researched cytokines. Tr. 21-22. When he moved to the University of Rochester School of Medicine and Dentistry, he led researchers who were exploring how vaccines “modulate the immune response.” Tr. 20-21. Ms. Koehn argues that Dr. McCabe’s specific training in immunology makes him “more qualified” than Dr. Rose “to discuss the effects of vaccines on cell biology.” Pet’r Reply Br. at 2-3.

Dr. McCabe is qualified to discuss immunologic principles and that expertise naturally fits in the discussion of theory under prong one of Althen. However, when those principles are applied to Vanessa specifically as part of the prong-two analysis, Dr. McCabe’s inexperience with diagnosing diseases in human beings becomes more problematic. Dr. McCabe does not have the experience of Dr. Rose, who has diagnosed and treated 150-200 patients with sJIA. Tr. 278. Thus, when it comes to evaluating their opinions, Dr. Rose’s opinion is given more weight.

Dr. Rose’s opinion is that Gardasil did not cause Vanessa’s sJIA. To him, Vanessa’s Gardasil vaccinations and her development of sJIA were “unrelated events.” Tr. 208. This opinion is persuasive.

#### **4. Summary**

The Althen prong two analysis is necessary only if it is found (or assumed) that the petitioner met the burden regarding Althen prong one. In the present case, Ms. Koehn’s evidence on prong one was not persuasive. Hence, the foregoing

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<sup>47</sup> Despite this argument, the Secretary did not file a Daubert-type motion to exclude his testimony. Such a motion to exclude testimony is relatively rare in the Vaccine Program. Fresco, 2013 WL 364723, at \*21; Garcia v. Sec’y of Health & Human Servs., No. 05-720V, 2010 WL 2507793, at \*2 (Fed. Cl. Spec. Mstr. May 19, 2010).

analysis about Vanessa's case was undertaken for the sake of completeness and to ensure that the entire record was considered.

The evidence about Vanessa does not persuasively show that she developed sJIA because of Gardasil. Her treating doctors gave her the third dose of Gardasil after she had been diagnosed with sJIA and the treating doctors continued to recommend other vaccinations to her. These vaccinations did not clearly exacerbate Vanessa's sJIA as might be expected if the Gardasil vaccine were causative.

As discussed in the context of Althen prong three, a sequence in which the vaccination preceded the development of the disease does not establish causation. In some cases, the disease followed the vaccination only as a matter of coincidence. See Capizzano, 440 F.3d at 1327 (recognizing the possibility of coincidence).

Dr. Verstraeten anticipated that coincidence and causation might be confused. He wrote:

Bearing in mind the background incidence of autoimmune disorders in adolescents and young adult population, it seems likely that, with broader use of HPV vaccines or other vaccines targeting this age group, autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship.

Exhibit E (Verstraeten) at 6633. Vanessa's case fits this description. Ms. Koehn has accurately reported that Vanessa's sJIA started after the vaccination but she has not established the necessary "causal relationship."

## **VII. Conclusion**

Through the testimony of Dr. McCabe, Ms. Koehn has presented some evidence on each of the Althen prongs. However, Dr. McCabe's opinions are not persuasive. Ms. Koehn has not established, under a more likely than not standard, that the two doses of Gardasil caused Vanessa to suffer sJIA.

She is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

**IT IS SO ORDERED.**

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