United States Court of Appeals for the Federal Circuit

CHERYL KOEHN, as Mother and Next Friend of, VANESSIA KOEHN,
Petitioners-Appellants,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,
Respondent-Appellee.

2014-5054

Appeal from the United States Court of Federal Claims in No. 1:11-vv-00355-EGB, Senior Judge Eric G. Bruggink.

Decided: December 4, 2014

P. LEIGH O'DELL, Beasley, Allen, Crow, Methvin, Prortis, & Miles, P.C., of Montgomery, Alabama, argued for petitioners-appellants.

DARRYL R. WISHARD, Trial Attorney, Torts Branch, Civil Division, United States Department of Justice, of Washington, DC, argued for respondent-appellee. With him on the brief were STUART F. DELERY, Assistant Attorney General, RUPA BHATTACHARYYA, Director, VINCENT J.

MATANOSKI, Deputy Director, and GABRIELLE M. FIELDING, Assistant Director.

Before MOORE, O'MALLEY, and REYNA, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* O'MALLEY.

Concurring opinion for the court filed by *Circuit Judge* MOORE.

O'MALLEY, *Circuit Judge.*

Cheryl Koehn appeals from a U.S. Court of Federal Claims judgment upholding a Special Master's denial of compensation for Koehn's daughter's systemic juvenile idiopathic arthritis ("SJIA") allegedly caused by a vaccine. Although the Special Master's assessment of Koehn's medical theory of causation contains several flaws, the Special Master had a sufficient basis upon which to determine that Koehn did not meet her burden of demonstrating a proximate temporal relationship between her daughter receiving the vaccine and developing SJIA. We therefore *affirm*.

BACKGROUND

Children with SJIA, an autoinflammatory disease, exhibit symptoms including arthritis, a fever, and a rash, and may experience flares involving similar symptoms as well as muscle and joint pain. Many of these symptoms result from dysfunctional production of proteins called cytokines, which certain cells release almost immediately after the body comes into contact with an antigen. Cytokines signal other cells to generate an immune response. Pro-inflammatory cytokines, like those associated with SJIA, can lead to fever or other inflammation. Examples of SJIA medication include prednisone, which reduces inflammation and suppresses the immune system, and etanercept, which inhibits a cytokine linked to SJIA.

Gardasil is a vaccine that immunizes against four strands of human papillomavirus ("HPV"). The vaccine, administered in three doses, contains virus-like particles created from an HPV protein, as well as an adjuvant, which assists in generating a robust immune response to promote long-term immunity.

I.

Koehn's daughter, Vanessia, was born in February 1995, and was generally healthy for the first twelve years of her life. Dr. Elena Regala administered Vanessia's first dose of Gardasil in February 2008 and her second dose in April 2008. On June 21, 2008, Vanessia experienced a rash all over her body. Dr. Regala, believing it to be an allergic reaction, prescribed Benadryl and prednisone three days later. Vanessia's rash disappeared within three days. On June 28, 2008, Vanessia went to Marian Medical Center for severe joint pain and high fever. Vanessia had stopped taking prednisone by that time, which coincided with her developing pain in her knees, thighs, and calves. Vanessia saw a rheumatologist at the hospital and received another prescription for prednisone. The hospital discharged her on July 2, 2008 with a presumptive diagnosis of juvenile idiopathic arthritis. Vanessia's only symptom at discharge was a rash.

On July 8, 2008, Vanessia saw Dr. Deborah McCurdy, a pediatric rheumatologist, who noted that Vanessia's family history included juvenile idiopathic arthritis and concluded that SJIA was a likely diagnosis. Dr. McCurdy communicated these findings to Dr. Regala, who administered Vanessia's third dose of Gardasil on August 19, 2008. Vanessia was no longer taking prednisone at that time, but had started taking etanercept. Vanessia experienced a flare of SJIA with fever, rash, and joint pain on August 25, 2008. In September 2008, Dr. McCurdy concluded that, though Vanessia had improved, she still showed signs of SJIA. Dr. McCurdy noted that Vanessia

complained of SJIA symptoms after she stopped taking prednisone, and that she had swollen ankles and knees.

II.

On behalf of Vanessia, Koehn filed an off-Table injury claim under the Vaccine Act. For off-Table injuries, which are those that do not appear on the statutory Vaccine Injury Table, 42 C.F.R. § 100.3 (2014), the petitioner must prove causation-in-fact. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1374 (Fed. Cir. 2009). A petitioner must prove the following by a preponderance of the evidence to establish causation: (1) a medical theory causally connecting the vaccination to the injury; (2) a logical sequence of cause and effect demonstrating that the vaccination caused the injury; and (3) a proximate temporal relationship between the vaccine and the injury. *Althen v. Sec'y of Health & Human Servs.* 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Koehn presented the opinion of Dr. Michael McCabe, who has a Ph.D. in microbiology and immunology and has researched environmental factors that affect immune response, to support her claim. Dr. McCabe asserted that Vanessia had a predisposition for SJIA, and that Gardasil was an environmental trigger because the vaccine caused a strong response in the same cytokines which are dysregulated in SJIA. He relied on several articles to support his theory, including an article discussing a study that tested cytokine levels in women who received an HPV vaccine on a three-dose regimen similar to Gardasil ("Pinto article"). In the study referred to by the Pinto article, researchers gave twenty female participants an HPV vaccine on the same three dose regimen as Gardasil, and drew blood before the first injection and one month after each of the second and third injections. The researchers either stimulated the blood samples with varying amounts of a virus-like particle in the vaccine or provided no stimulation at all. Cytokine levels were

relatively consistent in the vaccinated blood that received no stimulation. Cytokine levels increased, however, for the vaccinated blood that received the virus-like particle, and the elevated cytokines were the same as those dysregulated in SJIA. Dr. McCabe asserted that this commonality supports his theory that Gardasil triggered Vanessia's SJIA.

Dr. McCabe further testified that the lack of epidemiological studies on SJIA shows that the disease is too rare for scientists to be able to generate statistically relevant epidemiological data. As an example, Dr. McCabe presented an article discussing a study that evaluated the medical history of approximately 189,000 women to determine whether they developed an autoimmune response after receiving a quadrivalent HPV vaccine ("Chao article"). Though the Chao article did not find such a connection, Dr. McCabe relied on the article to demonstrate that SJIA is so rare that, despite the large sample size, it was not large enough to detect an increased rate of SJIA following HPV vaccination.

Finally, Dr. McCabe suggested that, because patients who receive Gardasil develop sufficient antibodies for immunity within seven months, Vanessia's development of SJIA within seven months after receiving Gardasil was evidence of a proximate temporal relationship.

The government's expert, Dr. Carlos Rose, is a pediatric rheumatologist and routinely treats children with SJIA, but has not researched the HPV vaccine or the role of cytokines in SJIA. Dr. Rose asserted that Vanessia's SJIA was more likely a coincidence. According to Dr. Rose, the most relevant results from the Pinto article were that the vaccinated blood samples with no stimulation had relatively consistent cytokine levels, whereas SJIA patients experience a pattern of up-regulated cytokine levels. Dr. Rose also cited an article referring to a study of roughly 60,000 individuals which found no in-

creased risk for autoimmune disorders for participants who received vaccines, including an HPV vaccine called Cervarix that uses a different adjuvant than Gardasil ("Verstraeten article").

III.

The Special Master denied Koehn compensation. The Special Master held that Koehn did not meet her burden under the first *Althen* prong, finding that Dr. McCabe's medical theory was unprecedented and had not been peer-reviewed or published. In addition, the Special Master found that the relevant scientific community, pediatric rheumatologists, did not accept Dr. McCabe's theory, primarily basing that conclusion on Dr. Rose's testimony that he, as head of pediatric rheumatology at his hospital, did not recall ever hearing of such a theory. The Special Master acknowledged that the Verstraeten article involved a different HPV vaccine than Gardasil and that its sample size was likely insufficient to produce statistically significant results. But, because Chao involved Gardasil and had more than double the sample size of the Verstraeten article, the Special Master held that the articles "[t]aken together" weighed against Dr. McCabe's theory. J.A. 143. Finally, the Special Master focused on the Pinto article's results indicating that cytokine levels increased only when the researchers stimulated the blood, and Dr. Rose's statement that "[o]f course when you stimulate with an antigen you get more cytokines released."

Moving to the second *Althen* prong, the Special Master held that Koehn did not establish a logical sequence of cause and effect between Gardasil and Vanessia's SJIA. In reaching this conclusion, the Special Master found Dr. Rose's opinion more persuasive because he is a doctor that treats patients, whereas Dr. McCabe does not treat patients.

The Special Master further held that Koehn did not meet her burden under the third *Althen* prong because

the record did not support Dr. McCabe's assertion that development of SJIA within a seven-month interval was sufficient to establish a proximate temporal relationship. Dr. McCabe reasoned that the onset of SJIA aligns with the time period during which Gardasil patients develop a sufficient immune response, which is seven months. The Special Master found, however, that both Dr. McCabe and Dr. Rose agreed that the immune system releases cytokines soon after the body encounters an antigen, which is inconsistent with Dr. McCabe's theory that onset of the disease could take many months. Dr. McCabe attempted to explain this contradiction by asserting that there is an "amplification process," but the Special Master concluded that he did not sufficiently support this explanation.

The Court of Federal Claims upheld the Special Master's decision. Koehn timely appealed. We have jurisdiction under 42 U.S.C. § 300aa–12(f) (2012).

DISCUSSION

In Vaccine Act cases, we apply the same standard of review that the Court of Federal Claims applied to the Special Master's decision. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010). Although we review legal determinations without deference, we review the Special Master's findings of fact under the arbitrary and capricious standard. *Griglock v. Sec'y of Health & Human Servs.*, 687 F.3d 1371, 1374 (Fed. Cir. 2012).

Though the Special Master had sufficient grounds to deny Koehn's petition because Koehn failed to meet her burden under the third *Althen* prong, we begin by recognizing that the Special Master committed several errors in the assessment of the first and second *Althen* prongs. As to the first *Althen* prong, for instance, the Special Master based his conclusion that the relevant scientific community did not accept Dr. McCabe's theory on Dr. Rose's statement that he did not recall ever hearing of

such a theory.[1] To impute Dr. Rose's anecdotal statement to the scientific community was wholly unreasonable. Another example is the Special Master's finding that, under the second *Althen* prong, Dr. Rose's opinion was more persuasive than Dr. McCabe's opinion because Dr. Rose treats patients and Dr. McCabe does not. We see no reasonable basis for why this distinction has any meaningful effect on the cause and effect inquiry in this case, and the Special Master provided none. While we recognize that it is within the Special Master's discretion to weigh the relevant evidence, the Special Master cannot manipulate the analysis in a manner calculated to arrive at a conclusion that he or she has already reached.

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[1] Had the Special Master properly evaluated the evidence, we believe the Special Master would have likely found that Koehn met her burden under the first *Althen* prong. The Pinto article demonstrated that the participants who received the HPV vaccine had increased levels of the same cytokines dysregulated in SJIA. Dr. Rose asserted that the article showed increased levels only when the vaccinated blood received a stimulus. Koehn explains, however, that measurement of cytokine levels can only occur in blood samples outside the body, and the only way to "replicate what is going on in the body" is to introduce an antigen to the blood sample assay. Oral Arg. at 5:24–6:56, *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2014-5054.mp3. A stimulus was therefore necessary to measure cytokine levels. Especially given the low incidence rate of SJIA, requiring a measurement without a stimulus would have compelled Koehn to present more than what is scientifically possible or legally necessary. Thus, Koehn likely presented a viable, "legally probable" medical theory that "there would only be an upregulation in cytokines [that are associated with SJIA] if those cells are told to do so [by the HPV vaccine.]" *Id.* at 6:50–6:56; *Moberly*, 592 F.3d at 1322.

Because Koehn failed to meet her burden under the third *Althen* prong, however, and failure to do so under any one of the *Althen* prongs is dispositive of this case, the Special Master correctly denied Koehn's petition.

We agree with the Special Master that Koehn's evidence failed to establish a proximate temporal relationship between Vanessia's Gardasil vaccine and development of SJIA under *Althen*'s third prong. This prong "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

The record did not support Dr. McCabe's suggestion that the appropriate timeframe for first exhibiting symptoms of SJIA caused by Gardasil can extend up to seven months. Dr. McCabe asserted that onset of SJIA can occur within seven months of receiving Gardasil because it normally takes patients seven months after receiving Gardasil to develop a sufficient immune response. Dr. McCabe did not, however, explain why the timing of SJIA onset aligns with the timing of a sufficient immune response in patients receiving the vaccine. Even Dr. McCabe agreed that the immune system produces cytokines quickly after the body encounters an antigen, which is inconsistent with his theory that onset of the disease could take many months. Dr. McCabe's position that the amount of time for developing sufficient antibodies for immunity after receiving a vaccine is always consistent with injury from the vaccine is a proposition that, without any evidentiary support, we simply cannot accept.

Koehn argues that Dr. McCabe explained this contradiction by referring to an "amplification process." But Dr. McCabe only speculated that there was a delay in the onset of SJIA because certain regulatory cells and in-

flammatory mediators in the body that are also purportedly active in response to an antigen may counteract the effects of cytokines, and admitted that "none of this was measured in" Vanessia. J.A. 232. We find the Special Master's conclusion that Dr. McCabe's explanation lacked sufficient support neither arbitrary nor capricious.

Thus, while we find fault with aspects of the Special Master's *Althen* analysis, we ultimately affirm his decision to deny compensation to Koehn. We agree that Koehn did not sufficiently establish why onset of SJIA can occur within seven months after receiving the first dose of Gardasil, especially when cytokine release is generally a more immediate response.

AFFIRMED

COSTS

No costs.

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MOORE, *Circuit Judge*, concurring.

I join fully in the majority's analysis of the third *Althen* prong. I recognize the strength of the reasons cited by the majority for being troubled by the Special Master's analysis on the first and second *Althen* prongs. I do not believe, however, that they present adequate grounds for reversal given the highly deferential standard of review we must apply.