In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 12, 2017

* * * * * * * * * * * * * *	PUBLISHED DECISION
ERIC P. CABRERA *and* CAROL CABRERA, *natural parents and guardians of* L.C., a minor,	
Petitioners,	No. 13-598V Special Master Gowen
v.	Entitlement; Diphtheria-Tetanus-Acellular Pertussis ("DTaP") Vaccine; Juvenile Idiopathic Arthritis ("JIA")
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
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Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for petitioners.
Darryl R. Wishard, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On August 21, 2013, Eric and Carol Cabrera ("petitioners") filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program"),[2] 42 U.S.C. § 300aa-10 et seq. (2012), on behalf of their minor child, L.C. Petitioners alleged that as a result of receiving a diphtheria-tetanus-acellular pertussis ("DTaP") vaccine on August 30, 2010, L.C. developed juvenile idiopathic arthritis ("JIA"). Petition at ¶ 3-4. Respondent recommended against awarding compensation. Respondent's ("Resp.") Report at 1.

[1] Because this published ruling contains a reasoned explanation for the action in this case, I intend to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to delete medical or other information, the disclosure of which would constitute a clearly unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

After a review of the entire record, I find that petitioners have provided preponderant evidence that the DTaP vaccination L.C. received on August 30, 2010, caused his JIA. Accordingly, petitioners are entitled to compensation.

I. BACKGROUND

A. Procedural History

Petitioners filed a petition on August 21, 2013, alleging that L.C. developed juvenile idiopathic arthritis as a result of receiving the DTaP vaccine on August 30, 2010. Petition at ¶ 3-4. Petitioners filed the expert report of Dr. Arthur E. Brawer, a rheumatologist, on May 12, 2014. See Petitioners' ("Pet.") Ex. 19. On September 26, 2014, respondent filed her Rule 4(c) report advising against compensation, along with the expert report of pediatric rheumatologist Dr. Carlos Rose and the medical literature referenced in his report. See Resp. Exs. A, D-F.

Petitioners filed a supplemental expert report from Dr. Brawer on November 10, 2014, along with medical literature. See Pet. Exs. 20-31. Respondent filed a supplemental expert report from Dr. Rose and the medical literature referenced therein on January 5, 2015. See Resp. Exs. G-J. Petitioners filed additional medical literature on October 19, 2015. See Pet. Ex. 45.

An entitlement hearing was held on Thursday, November 19, 2015, in Washington, D.C. Carol Cabrera and Dr. Brawer testified on behalf of petitioners, and Dr. Rose testified on behalf of respondent. Petitioners filed their post-hearing brief on February 24, 2016, and respondent filed her post-hearing brief on April 12, 2016. Petitioners filed a response to respondent's post-hearing brief on May 18, 2016. This matter is now ripe for adjudication.

B. Summary of Relevant Facts

L.C. was born on January 21, 2010. Pet. Ex. 3A at 8. A video from August 6, 2010, shows L.C. jumping in his jumper using both legs, and a video from August 21, 2010, shows him jumping and kicking in the water at the beach using both legs. Tr. at 23-24; Pet. Exs. 46, 49. On August 30, 2010, at 7 months of age, L.C. had a normal pediatric exam, met the appropriate developmental milestones, and received his first immunization, the DTaP vaccine. Pet. Ex. 16 at 25; Pet. Ex. 4A at 79; Tr. at 6-7, 29.

L.C. started crawling at the end of September 2010. Tr. at 7, 9. L.C.'s parents' affidavit states that "[a]bout three weeks to a month after the DTaP vaccine (end of September 2010), [L.C.] started crawling but not on both knees. His left knee was down on the ground and bent normally and his right knee was out to the side." Pet. Ex. 15 at ¶ 7; Tr. at 7. A video from September 29, 2010, shows him crawling with his right knee elevated, his right leg out to the side, and his left knee down normally. Tr. at 25; Pet. Ex. 47. At the time of the video, he had been trying to crawl for a few days. Tr. at 30. At first, his parents just thought he had a funny crawl, which they called his "crab crawl," and they did not bring it to the attention of health care providers or associate it with pain behavior. Id. at 7-8, 39. However, "about a month later (end of October 2010), [his parents] noticed that [L.C.] was having some pain in his right knee, and had been for about two weeks. He would not bear weight on his right leg when we would [try] to stand him up." Pet. Ex. 15 at ¶ 8; Tr. at 8, 38. By that time, he would also cry during diaper changes if they tried to straighten his leg at all. Tr. at 8. L.C.'s mother, Carol Cabrera, testified that about two weeks after he started crawling,

in mid-October, they noticed what they thought was pain in his leg during diaper changes and when they would stand him up. Id. at 31-32.

On October 26, 2010, L.C. visited his pediatrician, Dr. Cornelia Franz, for pulling on ears, runny nose, and fever. Pet. Ex. 16 at 24. At that visit, Dr. Franz noted "Dad states will not bear [weight] [right] leg since began standing, crawls funny." Id. On October 29, 2010, L.C. visited Dr. Franz again for his 9 month exam, and the record noted "won't bear [weight] [right] leg [for] 2 weeks." Id. at 23. He did not have any other illness between the time of the vaccine and the October 26 appointment.

On November 1, 2010, L.C. had a pediatric orthopedic consultation with Dr. Mark Birnbaum, who noted "L.C. comes in today for evaluation of a problem with his right leg which started approximately a week ago." Pet. Ex. 12 at 24. "The family originally noticed nothing until diaper changes when he was noted to have significant discomfort and guarding through his right knee region." Id. The impression was "probably occult or hairline Cozen fracture" and L.C. was placed in a leg cast for 2 ½ weeks. Id. L.C. did not improve after the casting, and on December 7, 2010, L.C. returned to Dr. Birnbaum with persistent complaints and not being able to do full weight bearing. Id. at 18; Tr. at 19-20. Dr. Birnbaum's record from December 7 notes that L.C. was seen for an injury at end of October, at which time "[r]eportedly, he had been in his bouncer seat and subsequently had discomfort." Pet. Ex. 12 at 18. The impression was "[p]ersistent right knee pain with limited motion" and he was sent for lab work and an MRI was ordered. Id. at 19. An MRI performed January 6, 2011, showed "small effusion and modest synovial hypertrophy." Pet. Ex. 14B at 92. L.C. had a positive anti-nuclear antibody ("ANA") test on February 21, 2011, and genetic testing was positive for the HLA-B27 gene. Pet. Ex. 16 at 14; Pet. Ex. 14C at 167. A repeat ANA test March 9, 2011, was negative. See, e.g. Pet. Ex. 4A at 50, 68.

On January 10, 2011, L.C. returned to the pediatric orthopedic office and saw Dr. Raymond Knapp. Dr. Knapp noted "[b]ack in October, [L.C.] had sustained an injury to his right knee. It was believed that this was a fracture." Pet. Ex. 16 at 27. He still had "persistent flexion of the knee and [would] not stand." Id. At another orthopedic visit on January 13, 2011, it was stated that "[t]he findings . . . remain consistent with probable inflammation and hypertrophy of the synovium of the knee following a likely viral illness." Pet. Ex. 12 at 13. A regimen of around the clock anti-inflammatories and physical therapy was implemented. Id. at 9.

Between October 26, 2010, and March 2011, L.C. had multiple ear infections, for which he took several different antibiotics. Tr. at 10-12, 34-35. L.C. also had a positive influenza A screen on October 29, 2010. Id. at 35; Pet. Ex. 16 at 23. On March 10, 2011, L.C. was admitted to the hospital for "knee swelling and limp, persistent fevers," and concern for possible septic joint. Pet. Ex. 14C at 125; Tr. at 13-14. The history states "[L.C.] is a 13 month old boy with a long history of recurrent fevers and limp. It all started in October 2010 when he started developing a limp." Pet. Ex. 14C at 125. He received IV antibiotics, which did not appear to help his knee. Tr. at 20. L.C. also underwent a repeat MRI of his bilateral knees on March 11, 2011, which revealed "[s]ynovial hypertrophy, small joint effusion, and extensive soft tissue swelling with enlarged lymph nodes posterior to the right knee. MR findings highly suggestive of a chronic inflammatory arthritic process." Pet. Ex. 14C at 172. L.C. was diagnosed with juvenile idiopathic arthritis during this hospitalization and was started on Celebrex and Prevacid. Tr. at 14-15, 17.

On March 22, 2011, L.C. had an initial pediatric rheumatology consultation with Dr. Melissa Elder M.D., who noted "a history of chronic right knee arthritis since September 2010 and recurrent otitis media since October 2010." Pet. Ex. 5 at 4. In a comprehensive history and evaluation, she reported: "[I]n 09/2010 he was noted to rather acutely develop a right knee flexion contracture. As per mother, he would no longer straighten his leg and would crawl without putting his right knee to the ground at all. He would not ever bear weight on it and he would cry when right knee was touched or attempts were made to straighten his knee." Id. Her impression was: "ANA positive, although repeat ANA was negative. HLA-B27 positive juvenile pauciarticular arthritis at least involving his right knee at this time, with significant flexion contracture. He may or may not have had mild inflammation of his left knee and bilateral hips, but on NSAIDs today and by MRI two weeks ago no inflammation was noted. He does not have systemic onset juvenile arthritis. Due to his delayed immunization status, I would like to avoid methotrexate for several months until his immunizations can be given, but he may need methotrexate to control his flexion contracture and probable leg length discrepancy. If he has uveitis on a slit lamp examination, then he has pauciarticular juvenile arthritis. I do not think that is septic arthritis, but I obviously cannot rule that out at this time." Pet. Ex. 4A at 13.[3] In May or June of 2011, Dr. Elder started L.C. on methotrexate, which he took for approximately a 9 week period without effect. Tr. at 21, 36-37. L.C. received a second DTaP vaccination on June 21, 2011. Id. at 35-36. His parents did not notice an increase in his right knee problems at that time. Id. at 36.

L.C. was evaluated by an ophthalmologist several times following his JIA diagnosis. See Pet. Ex. 11 at 45-46, 43-43A, 40, 42, 37-39, 34-36, 31-33, 28-30 (evaluations on March 31, 2011, June 23, 2011, September 30, 2011, November 17, 2011, February 24, 2012, May 21, 2012, August 29, 2012). On November 30, 2012, it was noted that he had "[l]ess sensitivity to light x several months," and had "keratic precipitates present in the left eye indicative of uveitis. His anterior chamber appears otherwise relatively quiet in each eye. This is the first time there has been any evidence of uveitis on exam." Id. at 27. L.C. was placed on prednisone acetate eye drops. Id. At visits on December 6 and 20, 2012, there was no evidence of uveitis. Id. at 21, 24. On February 19, 2013, the ophthalmologist again saw "evidence of mild keratic precipitates." Id. at 17. L.C. was re-started on prednisone acetate. Id. at 18. His mother testified that he did not have red eyes or any eye symptoms at the time keratic precipitates were observed, and no such symptoms are noted in the ophthalmology record. Tr. at 37, 39. L.C. was put on methotrexate again in early 2013. Id. at 37. L.C. continues to be treated for symptoms of JIA. Id. at 22.

II. STANDARDS FOR ADJUDICATION

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

[3] Dr. Elder could not rule out septic arthritis even though there was no evidence of infection at that time because L.C. had already been on a course of antibiotics when arthrocentesis was done. See Pet. Ex. 4A at 11.

To receive compensation under the Program, a petitioner must prove either a "Table" injury[4] or a causation-in-fact injury, i.e. that a vaccine listed in the Table was the cause in fact of an injury (an "off-Table" injury). See §§ 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). Petitioners allege L.C. suffered an "off-Table" injury. Therefore, petitioners must demonstrate by preponderant evidence that a covered vaccine is responsible for L.C.'s injury.

An "off-Table" injury is initially established when petitioner demonstrates by a preponderance of the evidence: (1) she received a vaccine set forth on the Vaccine Injury Table; (2) she received the vaccine in the United States; (3) she sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) the condition has persisted for more than six months. § 13(a)(1)(A). To satisfy the burden of proving causation in fact, petitioner must establish each of the three Althen factors by preponderant evidence: (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 proximate temporal relationship between vaccination and injury. Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); see de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each Althen factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See 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).

The Federal Circuit in Althen noted that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body."* Althen, 418 F.3d at 1280 (emphasis added).

Once petitioner establishes each of the Althen factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

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[4] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

In determining whether petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu v. Sec'y of Health & Human Services, 569 F.3d 1367, 1380 (Fed. Cir. 2009) (referencing Althen, 418 F.3d 1274; Capizzano, 440 F.3d 1317).

III. EXPERT OPINIONS

A. Expert Testimony

i. Petitioners' Expert, Dr. Arthur Brawer

Dr. Brawer was admitted as an expert in the field of rheumatology. Tr. at 48. He is board certified in internal medicine and rheumatology. Id. at 42. Dr. Brawer obtained his medical degree from the Boston University School of Medicine in 1972. Id. at 41. He then completed an internal medicine residency and arthritis fellowship, and began practicing rheumatology in 1976. Id. at 41-42. He has a private rheumatology practice in Long Branch, New Jersey, and also runs the arthritis clinic at Monmouth Medical Center. Id. at 42-44. He treats adult and pediatric patients in both practices. Id. Dr. Brawer is an associate clinical professor at Hahnemann/Drexel University School of Medicine, in Philadelphia, Pennsylvania, and an assistant clinical professor of medicine at Robert Wood Johnson University School of Medicine, in New Brunswick, New Jersey. Id. at 42. He sees patients with juvenile idiopathic arthritis, but has not treated any under the age of 12 months in the last year. Id. at 45.

a. Althen Prong I

Dr. Brawer opined that JIA is "capable of being directly initiated by one or more immunizations." Pet. Ex. 19 at 4. Dr. Brawer testified that there are many "triggers" of JIA, including trauma and physical injury, infection, vaccination, extreme temperature changes, severe emotional upset, and insecticides, pesticides, and fungicides. Tr. at 49-50. These "triggering" events initiate different pathways of inflammation (all of which are different than in the standard idiopathic case), which eventually "converge on the common pathway," whereby an autoimmune disorder is caused. See id. at 53-56. Dr. Brawer testified that researchers recently looked at the question of who is at risk for vaccine-induced autoimmunity, and some authors think that some genetically at-risk populations are more susceptible to developing an autoimmune disorder such as

JIA.[5] Id. at 94-95, 97. These susceptible individuals include people who have family members with autoimmune diseases, patients who already have an autoimmune disease, and patients who are asymptomatic carriers of the markers of autoimmunity (such as HLA-B27, ANA, and rheumatoid factor). Id. at 94, 97. In addition, Dr. Brawer stated that one study suggested that the HLA-B27 antigen is more likely a marker of who will react adversely to vaccines rather than a marker for an arthritis condition. Id. at 94-95; Pet. Ex. 20 at 2 (citing Pet. Ex. 23[6]). Thus, Dr. Brawer's testimony was that an environmental trigger in a genetically susceptible individual could initiate the disease process of JIA.

Dr. Brawer stated that molecular mimicry "has been in the differential of things that cause idiopathic rheumatoid arthritis in juveniles for decades." Tr. at 85. On a basic level, molecular mimicry posits that when a virus or infection enters the body, the body produces antibodies that react not only to the infecting agent but also cross-reacts with self-antigens present on a variety of body cells, thereby producing autoimmune disease. Id. at 85. Dr. Brawer stated that the mechanism of molecular mimicry as a cause of autoimmunity has been published in the medical literature for at least 27 years and continues to be researched. Id. at 113. In certain spontaneous disorders, molecular mimicry has been demonstrated between self-antigens and a retained virus in the body, and Dr. Brawer cited these disorders in support of the fact that mimicry can trigger autoimmunity. Id. at 88. In lupus, for example, patients produce an antibody that cross-reacts with a nucleotide sequence of their own RNA and genetic material of the Epstein-Barr virus. Id. at 86. Based on this, Dr. Brawer queried: "if molecular mimicry is good enough as a potential explanation for the onset of autoimmune diseases, why would it not be good enough as a potential explanation for the onset of vaccine-induced injury?" Id. at 87. With vaccinations, antigenic components of a virus are injected in the hope that the immune system will elicit an antibody response to them, and Dr. Brawer stated that "[i]t has been known for over 20 years that there exists a cross-reactivity between routinely used vaccine materials and self-antigens in the body." Id. at 87; Pet. Ex. 20 at 2.

In an Order dated October 10, 2014, Dr. Brawer was asked to supply evidence of homology between the DTaP vaccine and tissue in human joints and to provide an opinion as to the sufficiency of such homology to explain vaccine causation of JIA. See Order, dated October 10, 2014, at 1. In response, Dr. Brawer submitted an article by Sutjita et al, "Polyspecific human and murine antibodies to diphtheria and tetanus toxoids and phospholipids." See Pet. Ex. 20 at 1 (submitting Pet. Ex. 21[7]).[8] Dr. Brawer testified that according to this article, the potential for phospholipids

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[5] Dr. Brawer later testified, however, that he believes genetics may determine how mild or severe the disease is going to be in a particular individual, *not* whether they get it at all. Tr. at 141. Nevertheless, he was consistent in his opinion that JIA is not explained by genetic factors alone.

[6] Pet. Ex. 23, T. Vial & J. Descotes, *supra* note 13 ("[t]he presence of HLA-B27 antigen in the majority of patients who developed rheumatoid arthritis suggests a possible role of vaccination in susceptible individuals.").

[7] Pet. Ex. 21, M. Sutjita et al, *Polyspecific Human and Murine Antibodies to Diphtheria and Tetanus Toxoids and Phospholipids*, 73 CLIN. EXP. IMMUNOL. 191 (1988).

[8] Dr. Brawer also submitted as Pet. Ex. 22, D. Kanduc, *Quantifying the Possible Cross-Reactivity Risk of an HPV16 Vaccine*, 8 J. OF EXPERIMENTAL THERAPEUTICS AND ONCOLOGY 65 (2009). In addition, he submitted Pet. Ex. 45, M. Stojanović et al., *Role of Molecular Mimicry and Polyclonal Cell Activation in the*

(which are a component of the membrane of all body cells) to be mimics to diphtheria and tetanus toxoid exists. Tr. at 115-16. For genetically susceptible individuals, if there is a potential mimic to diphtheria and tetanus, the immune response would react to both the phospholipids in the body as well as the injected antigens. Id. at 118. Dr. Brawer did not, however, identify specific homology between the DTaP vaccine and human joint tissue. Further, on cross-examination, Dr. Brawer agreed that the Sutjita article does not identify any specific antigen in the DTaP vaccine that would cross-react with human joint tissue, and stated that he does not know the exact components of the DTaP vaccine. Id. at 145-46. When asked what antibodies, specifically, would produce the damage and inflammation in L.C.'s joints to cause JIA, he responded that "[i]f we knew the exact antibody or antibodies or processes that trigger the disease, then we would know the cause." Id. at 135.

Although his expert reports focused on molecular mimicry, at hearing Dr. Brawer stated that molecular mimicry in a genetically susceptible person was just one of a number of different possible mechanisms that may cause an autoimmune disorder such as JIA. Tr. at 102. Molecular mimicry "may not be sufficient; it may not be the only process," or "there may be many predisposing factors that trigger the disease." Id. Multiple mechanisms could be occurring in concert with one another. Id. at 122. On cross-examination, Dr. Brawer was hesitant to commit to one mechanism to explain L.C.'s case. When asked if there was one particular mechanism he was relying on, Dr. Brawer responded "[n]o," and that he "think[s] there are many pathways that lead to a chronic illness that we recognize as rheumatoid arthritis." Id. at 140-41. Asked if mimicry would be "at the top of [his] list in terms of theories that would be applied to L.C.'s case," Dr. Brawer responded that "[i]t seems to be the hot issue at the top of the list. It doesn't necessarily mean that it's at the top of my list," and that he "like[s] to take into account all possibilities." Id. at 142. Finally, when pressed to express a theory that explains this particular case in some way, not one that simply works in general, Dr. Brawer responded: "mimicry theory has to be right now at the top of the list" because mimicry is "starting to gain traction with the natural-occurring disease. So, if it has relevance for that, why should it not have relevance for a vaccine-induced autoimmunity?" Id. at 144-45.

b. Althen Prong II

Dr. Brawer opined that L.C.'s JIA was "directly initiated by the DTaP vaccine administered on August 30, 2010." Pet. Ex. 19 at 3. Dr. Brawer testified that L.C. does not fit into any of the defined categories of spontaneous onset JIA, and thus there must have been some other trigger or predisposing factor—in this case, the DTaP vaccine. Tr. at 65-66.

Dr. Brawer explained that approximately 40 years ago, the presentation of JIA was initially defined into five categories: (1) patients with Still's disease; (2) patients around 6 years old with a positive ANA test about 25% of the time; (3) patients between 10 and 13 years old; (4) female patients between 1 and 3 years old, about 40% of whom had a positive ANA test and about 40% of whom developed posterior uveitis; and (5) male patients between 10 and 15 years old, some of whom went on to develop ankylosing spondylitis, and who might develop anterior uveitis. Tr. at

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Induction of Pathogenic β2-Glycoprotein I–Directed Immune Response in Balb/c Mice Upon Hyperimmunization with Tetanus Toxoid, 56 IMMUNOL. RES. 20 (2013). Dr. Brawer testified that this article says that hyper immunization with tetanus is triggering the development of more than one type of antibody. Tr. at 119-20.

58-61, 68; Pet. Ex. 19 at 5. In addition, the HLA-B27 marker was noted in the 1980s. Tr. at 69. The prevalence of HLA-B27 in the first four groups is the same as it is in the general population, 6-8%, but it is associated with the fifth category. Id. at 68-69. Dr. Brawer emphasized that the categories are not neat categories, that there is some overlap, and that modern textbooks use different nomenclature.[9] Id. at 62-63.

The closest match to L.C.'s presentation is the fourth category, Dr. Brawer said. However, that category is comprised of "almost exclusively" female patients. Tr. at 65. In addition, the patients in this category are not HLA-B27 positive. Rather, positive ANA is the predominant marker. Id. at 66. L.C., however, *is* HLA-B27 positive, and while he was initially ANA positive, he was ANA negative on a subsequent test.[10] Id. Further, Dr. Brawer opined that L.C. does not have uveitis.[11] Id. Thus, L.C. is a mismatch for this category in terms of sex, the fact that these female patients are ANA positive and B27 negative, and the fact that many have uveitis. Id.

Similarly, Dr. Brawer opined that L.C. is the wrong age to fit into the fifth category, the enthesopathy spondylopathy category (or what Dr. Rose refers to as Enthesitis Related Arthritis ("ERA")[12]), because he was too young and did not have anterior uveitis. Tr. at 69, 79-80; Pet. Ex. 20 at 2. Dr. Brawer explained that uveitis is inflammation of the pigmented layers of the eye. Tr. at 71-72. Anterior uveitis is synonymous with iritis (inflammation of the iris) and is usually painful

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[9] It is not clear why Dr. Brawer relied on the old criteria for his report and testimony. As discussed below, respondent's expert, Dr. Rose, relied on the newer International League of Associations of Rheumatology ("ILAR") criteria. Nevertheless, the experts largely agreed on the criteria for the relevant categories of JIA, particularly ERA. Therefore, any difference between the old versus new classification systems for purposes of this Ruling are largely semantic.

[10] Dr. Brawer stated that L.C. is ANA negative. However, L.C. did have a positive ANA test on February 21, 2011. Pet. Ex. 16 at 14.

[11] This opinion is in contrast to the opinion Dr. Brawer offered in his first expert report, in which he stated that L.C. had posterior uveitis. See Pet. Ex. 19 at 5.

[12] ILAR classifications define 7 subgroups of JIA, one of which is ERA. Resp. Ex. G at 2. This is a newer classification system than the system that Dr. Brawer relied on, which Dr. Rose indicated was the "Park City" criteria from 1977. Tr. at 155-56. Enthesitis is an inflammation of the muscular or tendinous attachment to bone. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 627 (32nd ed. 2012). The For a diagnosis of ERA, the ILAR criteria require arthritis and enthesitis *or* arthritis and at least two of the following additional symptoms: sacroiliac joint tenderness; presence of HLA-B27; family history in at least one first- or second-degree relative with medically confirmed HLA-B27 associated disease; anterior uveitis that is usually associated with pain, redness, or photophobia; and the onset of arthritis in a boy after 8 years of age. Resp. Ex. A at 6; Resp. Ex. C at 3. Resp. Ex. C, J. CASSIDY ET AL., TEXTBOOK OF PEDIATRIC RHEUMATOLOGY 273 (6th ed. 2011). Dr. Rose noted in his expert report that the terms ERA and pediatric spondyloarthropathy are used interchangeably. Resp. Ex. G. at 1-2. ERA is the terminology used in the ILAR, and spondyloarthropathy is the older terminology used by Dr. Brawer.

and red.[13] Id. at 71-72. Signs of anterior uveitis on exam would be inflammation of the iris, white cells in the anterior chamber during active uveitis, and keratic precipitates (deposits of inflammatory cells and debris in the cornea that can be seen following active inflammation). Id. at 74-75, 158. Dr. Brawer noted that L.C. did not have a red eye, did not complain about pain, and no white cells were seen on slit lamp exam that would indicate active uveitis. Id. at 75, 78. He did have keratic precipitates in the left eye seen in November 2012, but not before. Dr. Brawer noted that it is not described whether they were on the endothelial or epithelial surface of the cornea, and there are many causes of keratic precipitates in addition to uveitis, such as trauma to the eye. Id. at 75-76. The anterior chamber was also noted to be "quiet." Pet. Ex. 11 at 27. Thus, Dr. Brawer stated that it is not possible to conclude that the keratic precipitates were necessarily due to uveitis. Tr. at 308. Keratic precipitates are not diagnostic of uveitis, but rather are the result of an injury to the eye, for which there can be many causes. Pet. Post-Hearing Brief at 16. Dr. Brawer opined that the treating ophthalmologist was in error when he stated that L.C. manifested uveitis based solely on the finding of keratic precipitates, and none of the other signs or symptoms of uveitis. Pet. Ex. 20 at 3.

Based on his opinion that L.C. did not have anterior uveitis, Dr. Brawer concluded that L.C. does not meet the criteria for ERA. Tr. at 309. According to Dr. Brawer, the importance of whether L.C. has ERA is that whether JIA is an antibody-mediated disease—and thus whether molecular mimicry is relevant—depends on the subgroup. Id. at 133. Typical, non-ERA, JIA is considered autoimmune in nature, whereas ERA is considered autoinflammatory. Id. at 313-14. Thus, Dr. Brawer stated that if L.C. did not have ERA, Dr. Rose's explanation of the autoinflammatory mechanisms of the HLA-B27 pathway, discussed below, would be inapplicable. Id. In addition, if L.C. had non-ERA JIA, HLA-B27 is not at all relevant to causation of the disease. HLA-B27 is a risk factor in the ERA subset of JIA, but not for the other categories of JIA. Id. at 314.

Finally, Dr. Brawer opined that L.C.'s JIA is not explained by an alternative environmental cause, such as infection. Pet. Ex. 19 at 4; Tr. at 137-38. Dr. Brawer acknowledged that from late October 2010 through March 2011, L.C. had recurring ear infections and had a positive influenza A test on October 29, 2010. Tr. at 136. However, Dr. Brawer opined that these infections were not the trigger for L.C.'s JIA. Id. at 136-37. This opinion was based on the fact that Dr. Brawer put the onset of L.C.'s JIA in late September 2010, prior to the infections, for the reasons discussed below as part of Althen Prong III. Id. at 139.

c. Althen Prong III

Dr. Brawer opined that L.C.'s JIA began no later than three weeks after the vaccine administration on August 30, 2010. Pet. Ex. 19 at 3; Tr. at 123. Dr. Brawer's opinion regarding onset was based on the history given by L.C.'s parents, the videos of L.C. crawling, the ultimate chronicity of L.C.'s issues, and the histories recorded in the medical records. Tr. at 139-40. In

[13] Posterior uveitis, on the other hand, is essentially choroiditis in the back of the eye, and is usually painless. Tr. at 72.

particular, Dr. Brawer focused on the way L.C. was crawling when he began crawling in late September. Id. at 123-24. Dr. Brawer stated that some children do a "crab crawl" when they first begin crawling and there is nothing wrong with them. Id. at 125. However, in the context of L.C.'s subsequent history, which included parental accounts of apparent pain while having his leg straightened out during diaper changing and difficulty bearing weight when standing, Dr. Brawer concluded that the "crab crawl" was pain behavior. Id. at 124-26, 312. In addition, as to the contemporaneous medical records that put onset in mid-October, Dr. Brawer stated that "orthopedic notes on patients with arthritis with regards to the chronological evolution of the problem are notoriously inaccurate," and that he would weigh the rheumatology record, which puts onset in September, over the orthopedic records despite the fact that the orthopedic records were created closer in time to the onset of the disease. Id. at 310-11. Dr. Brawer opined that the video that Dr. Rose said showed L.C. extending his leg fully does not exclude the development of arthritis in September because symptoms wax and wane at the beginning of the disease onset. Id. at 312. More importantly, Dr. Brawer opined that L.C.'s knee was *not* fully extended in the September video, and that he thought that there was at least a 20-degree flexion contracture at that point. Id. Dr. Brawer also noted that there is a difference between the actual onset of the disease as opposed to when you are able to make the diagnosis based on chronicity. Id. at 56. Dr. Brawer did not offer an opinion as to whether a timing of onset three weeks after vaccination would be appropriate assuming that molecular mimicry was the mechanism of causation. However, in his first expert report, he did suggest that when viewed retrospectively in light of the entire history, the timing was appropriate given the chronology of events, with no other cause intervening between the vaccination and the onset of symptoms in September. Pet. Ex 19 at 5.

i. Respondent's Expert, Dr. Carlos Daniel Rose

Dr. Rose was admitted as an expert in the field of pediatric rheumatology. Tr. at 154. He is board certified in pediatric rheumatology. Id. at 150. Dr. Rose received his medical degree from the University of Buenos Aires School of Medicine in 1977, and completed a residency in internal medicine and fellowship in adult rheumatology at the University of Buenos Aires Hospital. Id. at 148-49; Resp. Ex. K at 1, 5. He then did a pediatric residency at Thomas Jefferson University, in Philadelphia, a fellowship in pediatric rheumatology at Children's Hospital of Philadelphia, and a year of rotation focused on rheumatology at DuPont Children's Hospital in Wilmington, Delaware. Tr. at 149; Resp. Ex. K, at 5. Dr. Rose has been the chief of the division of pediatric rheumatology at DuPont Children's Hospital since 1994, and is a professor of pediatrics at Thomas Jefferson University. Tr. at 148. Dr. Rose treats pediatric patients in the division of pediatric rheumatology at DuPont Children's Hospital. Id. at 152. The division as a whole manages several hundred patients with juvenile idiopathic arthritis. Id. He lectures about JIA and has published numerous papers on the subject. Id. at 153; See Resp. Ex. K at 13-43.

a. Althen Prong I

Dr. Rose agreed that molecular mimicry is a mechanism of autoimmunity that has been established in at least one autoimmune condition—rheumatic fever—and has been postulated for many others. Tr. at 265-66. However, he did not believe L.C.'s case was a result of molecular mimicry, because the ERA sub-category of JIA, which he opined L.C. had, falls on the

autoinflammatory, rather than autoimmune, end of the disease spectrum. Id. at 175, 267. This is a different mechanism from the antibody-mediated theory of disease and in this case has to do with inflammation resulting from the misassembling of HLA-B27. Id. at 170. Dr. Rose stressed that while HLA-B27 is a normal variant seen in 8 percent of the Caucasian population, it is highly associated with the ERA form of JIA. Id. at 158, 163. Everyone has an HLA-B type, and B27 is a subtype. Id. at 164. HLA-B is inside the cell and responds to intracellular infection by travelling through the cell to the cell surface to expose a piece of peptide of the agent that infected the cell, and calls for CD8 T-cells to kill the cell. Id. at 165. The B27 subtype is not good at assembling itself inside the cell. Id. at 167. When it travels from the inside of the cell to the outside, it misassembles itself, which elicits an inflammatory response. Id. Thus, Dr. Rose testified that he did not believe molecular mimicry was involved in L.C.'s case primarily because L.C.'s ERA disease was not on the autoimmune end of the disease spectrum.

Dr. Rose also provided several other reasons he did not think molecular mimicry was the mechanism in this case. He stated that in order to think that the mechanism was molecular mimicry, he would like to see an immediate innate response to the vaccine, such as fever or some event, and/or "an animal experiment in real mice where you have injected them with the corresponding equivalent dose of the same that L.C. got [sic], and to have the[m] develop something that mimics arthritis or uveitis." Tr. at 267. In addition, Dr. Rose wrote in his expert report that in order to demonstrate molecular mimicry as a disease mechanism, protein or peptide homology between components of DTaP and human tissue in question should be found first. Resp. Ex. A at 10-11. Dr. Rose stated that in reviewing the product insert of the DTaP vaccine, he did not see "any protein that called my attention to be replicable to human synovial tissue." Tr. at 172. In addition, other than the pertussis component, which could have phospholipids, "none of the toxoid of diphtheria, nor the toxoid of tetanus, seem to contain phospholipids." Tr. at 173.

Dr. Rose stated, however, that while JIA is thought to be mostly genetic and the genetic markers of JIA add a risk factor, the genetics are non-Mendelian genetics where you need four or five of the relevant genes to reach the critical mass to develop the disease. Tr. at 180. HLA-B27 confers a significant risk of developing ERA, but not everyone with HLA-B27 develops ERA. Id. at 181-83. Dr. Rose testified that the thinking as to why some percentage of those with HLA-B27 develop ERA and some don't is that the B27 variant works with other gene variants or molecules to produce the disease. Id. at 186-87. When asked whether, alternatively, it is possible that a gene is affected by an exogenous factor that then triggers the autoimmune response, Dr. Rose stated that the idea that an individual "may encounter the right environmental factor any day and given the four or five genes that they have, mount an abnormally exaggerated, or even perpetrating," inflammatory response is "the clear thinking in juvenile arthritis." Id. at 181. Thus, while Dr. Rose focused on the idea that multiple genes could interact to cause the disease, he also agreed that an environmental factor most likely interacts with genetics in a susceptible individual to produce disease. He stated that in his opinion, environmental factors do play a role in the development of JIA, and it is not a genetic disorder only. Id. at 254.

b. Althen Prong II

Dr. Rose opined that L.C.'s vaccination had no relationship with his JIA. Rather, his disease was "spontaneously and genetically determined." Tr. at 155, 158; Resp. Ex. A at 13. Dr. Rose opined that L.C.'s JIA meets the ILAR criteria for enthesitis-related arthritis ("ERA"). Id. at 158. For a diagnosis of ERA, the ILAR criteria require arthritis and enthesitis *or* arthritis and at least two of the following additional symptoms: sacroiliac joint tenderness; presence of HLA-B27; family history in at least one first- or second-degree relative with medically confirmed HLA-B27 associated disease; anterior uveitis that is usually associated with pain, redness, or photophobia; and the onset of arthritis in a boy after 8 years of age. Resp. Ex. A at 6; Resp. Ex. C at 3.[14] In this case, Dr. Rose stated, L.C. had arthritis of the knee, is HLA-B27 positive, and had acute anterior uveitis. Tr. at 158. Thus, Dr. Rose opined that "[t]his looks like a garden-variety JIA, in all ways" although he admitted that "[t]he age is perhaps on the left side of the curve," as he does not meet the criteria of being over age 8.[15] Id. at 162. In addition to the above criteria, ERA is "characterized by the absence of autoantibodies such as rheumatoid factor (RF) and antinuclear antibodies (ANA) and by a strong association with the human leukocyte antigen-B27 (HLA-B27)." Resp. Ex. C at 2. Dr. Rose opined that L.C. had "typical albeit rather early onset [JIA], probably ANA negative[16] and associated with a positive HLA-B27. The male gender and the episode of acute anterior uveitis (AAU) suggests that he has the Enthesitis Related Arthritis (ERA) type of JIA. Overall there is nothing atypical or unusual in his clinical picture." Resp. Ex. A at 7.

Unlike Dr. Brawer, Dr. Rose opined that L.C. had anterior uveitis. Tr. at 158. Dr. Rose stated that the absence of fluid or debris in the anterior chamber on exam was due to the fact that the uveitis was caught after the acute flare, and the keratic precipitates were sequelae left after the acute event. Id. at 158-59, 220-21. Because, anterior uveitis in ERA is acute and goes in phases, it is likely that L.C.'s uveitis was caught between episodes. Id. at 161. While he acknowledged that keratic precipitates can be caused by things other than uveitis, such as a corneal scratch, he emphasized that there was a consensus among the treating ophthalmologists that L.C. had uveitis. Id. at 159. Dr. Rose opined that the presence of the keratic precipitates by themselves, without redness of the eye, pain, or other symptoms of uveitis, was enough for the treating physician to make the diagnosis of uveitis in this case. Id. at 161-62. Dr. Rose stated that he has never seen it specified in ophthalmologic reports whether keratic precipitates were on the epithelial or endothelial side of the eye. Id. at 217.

Ultimately, however, and in contrast to Dr. Brawer's opinion that whether L.C. had ERA was crucial to determining whether this was an autoimmune or autoinflammatory process and whether HLA-B27 played a role in causation, Dr. Rose stated that "it doesn't have that much of a bearing" whether L.C. has ERA or another subcategory of JIA. Tr. at 223. Dr. Rose stated that autoimmune and autoinflammatory diseases are on a spectrum, but spondyloarthropathies such as ERA are more autoinflammatory and other JIAs are autoimmune. Id. at 224. The difference between autoinflammatory and autoimmune diseases involves CD8 T-cells versus CD4 T-cells, respectively. Id. at 225. Predominantly autoantibody-mediated disease (CD4, T-Cell, B-cell) are

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[14] Resp. Ex. C, J. CASSIDY ET AL., TEXTBOOK OF PEDIATRIC RHEUMATOLOGY 273 (6th ed. 2011).

[15] Dr. Rose stated "age six" in his testimony, but the ILAR criteria refer to age 8. See Tr. at 162; Resp. Ex. C at 3.

[16] Although Dr. Rose characterized L.C. as "probably ANA negative," he later stated that he considered L.C.'s positive ANA test because that determines the risk of uveitis. Tr. at 245.

on one side, and natural killer, CD8 cells and cytokines on the other. Id. at 248. Autoinflammatory disease arises out of the function of the innate immune system and cytokine signaling, whereas the autoimmune disease arises from the adaptive T-cell and B-cell response. Id. at 225-26. Thus, it is a different arm of the immune system affected in ERA as opposed to JIA. Id. at 226. Dr. Rose emphasized, however, that autoimmune and autoinflammatory fall on a spectrum, but that there are more features of ERA that put it in the autoinflammatory end. Id. at 227, 247. However, he stated that he is not denying that L.C. has autoimmunity features, such as a positive ANA test. Id. at 316.

c. Althen Prong III

Dr. Rose opined that the contemporaneous medical records and videos of L.C. crawling indicate that the onset of L.C.'s JIA occurred in late October 2010, approximately 7 weeks post-vaccination. Resp. Ex. A at 8; Tr. at 201. Because Dr. Rose opined that the onset of L.C.'s JIA occurred in late October 2010, Dr. Rose indicated that the ear infections and positive influenza A screen around the end of October 2010, concurrent with onset, should be looked at as alternative causes. Tr. at 198-99. In addition, Dr. Rose stated the length of time between the alleged trigger and the clinical onset appears too long for molecular mimicry to be the mechanism of causation. Resp. Ex. A at 11. For diseases in which molecular mimicry is an accepted mechanism, such as acute rheumatic fever, a four-week latency period is expected. Id.

Dr. Rose stated that "[t]he most common or the most important element in the diagnosing of arthritis in the pre-walking era . . . is flexion contracture," which is "produced by the contraction of the flexor muscles, in this case the hamstrings, that are responding via the cord, the nervous system, with contraction of the joint." Tr. at 202. It is not necessarily a pain mechanism. Id. at 203. Dr. Rose stated that in his experience, "mono-arthritis of the knee in infants becomes obvious either as a delay in ambulation or as a result of findings during routine manipulation such as dressing or bathing." Resp. Ex. G at 1.

Dr. Rose noted that Dr. Knapp's note from November 1, 2010, stated that L.C.'s parents "noted discomfort with diaper changes a week earlier," and this date of onset is reiterated in Dr. Knapp's notes from January 10, 2011, and February 21, 2011. Resp. Ex. G at 1. Dr. Birnbaum's record from December 7, 2010, notes that L.C. was seen for an injury at the end of October, at which time "[r]eportedly, he had been in his bouncer seat and subsequently had discomfort." Id. (referencing Pet. Ex. 12 at 18). Diaper changes and bouncing on a bouncer seat are both associated with knee flexion and extension. Id. at 2. There was never any evidence of a trauma or injury giving rise to this condition.

Dr. Rose further stated that the video of L.C. crawling in September 2010 looks like normal crawling for a baby that is starting to crawl. Tr. at 201 (referring to Pet. Ex. 47). Dr. Rose said that in his clinic, he has his patients crawl or walk as part of the physical exam. Id. at 201-02. In particular, Dr. Rose noted that in the September video, L.C. at one point extends the right knee fully. Therefore there is no flexion contracture at the time of the video. Id. at 206. If L.C. had a contracture, it would have been "impossible" for him to even momentarily break through it. Id. at 208. When asked if it was possible that in the September video, L.C. was exhibiting early compensation to pain, and responding to the compression of the knee between the knee and the floor, Dr. Rose again responded that extension of an inflamed knee is impossible. Id. at 211-12.

Dr. Rose concluded that because L.C. had full extension of the knee, he would not say that L.C. had arthritis of the knee at that time. Id. at 212.

Dr. Rose opined that infection was a more likely cause of L.C.'s JIA than the vaccine. Tr. at 271. Dr. Rose noted that during October 2010, L.C. suffered from ear infections. Resp. Ex. A at 8. Although JIA is primarily genetic, "if one is to consider the merits of stimulation of the immune system, common sense dictates that concurrent ear infections rather than a remote non-arthritogenic stimulant of the immune system, namely DTaP vaccination, are more likely culprits." Id. at 9. Dr. Rose stated that even if there were no infections before onset, there still could have been other environmental factors that remained unidentified, such as viral infections that were unnoticed, that there is no evidence in the literature for vaccine induced JIA, and he would still not think the vaccine was the trigger, although he acknowledged that a vaccine would be considered an environmental factor. Id. at 305, 317.

IV. EVALUATION OF THE EVIDENCE[17]

Petitioner contends that the DTaP vaccine L.C. received on August 30, 2010, caused the onset of his JIA, the onset of which was evident by about the third week of September. Respondent disputes that the DTaP vaccine caused or substantially contributed to the onset of L.C.'s JIA, the onset date of L.C.'s symptoms, and that L.C.'s symptoms occurred within an appropriate timeframe following vaccination. Joint Pre-Hearing Submission at 2. Accordingly, all three prongs of Althen are at issue in this case. The legal issues to be resolved are whether petitioners have put forth preponderant evidence of: (1) a reliable medical theory causally connecting L.C.'s DTaP vaccination with his JIA; (2) a logical sequence of cause and effect showing that L.C.'s DTaP vaccination was the reason for his JIA; and (3) a proximate temporal relationship between L.C.'s DTaP vaccination and his JIA. If petitioner puts forth preponderant evidence of the foregoing elements, respondent has the burden to show whether otitis media (an ear infection) and influenza, which L.C. suffered in late October, were alternative causal factors in causing the child's JIA.

Much of the expert testimony in this case was confusing at best, in part because this case involves a rare presentation of an uncommon disease. It appears that some of the criteria for diagnosis of this disease or the subcategories thereof have recently been evolving in the rheumatology community and that, as is true with many autoinflammatory diseases, the causal factors of the disease remain in the realm of the theoretical. Some of the confusion no doubt arose because of the quest for specificity and certainty in understanding causation that we see in this Program, when there is at most consensus that underlying vulnerabilities most likely combine with an environmental trigger to produce juvenile rheumatoid arthritis. Dr. Rose agreed with the statement made in Respondent's Exhibit E, which he referred to as the article by Dr. Wraith, that of the many potential environmental factors, infections are the most likely, and "[m]icrobial antigens

[17] I have considered the entire record in arriving at my decision (§ 300aa–13(a)(1)). This includes medical literature submitted by both parties, which I have read and considered. I will discuss in the course of this opinion the exhibits that are most relevant to the resolution of this case.

can induce cross-reactive immune responses against self-antigens, whereas infections can non-specifically enhance their presentation to the immune system." Tr. at 257-58.[18]

It is clear that both doctors in this case agree that L.C. has JIA in his right knee. Tr. 133, 155. There is no controversy on that point, and after the diagnosis was initially reached there has been no disagreement among the treating physicians either. The term "pauciarticular juvenile rheumatoid arthritis" has been used to describe L.C.'s condition because his arthritis is present in fewer than four joints. Tr. at 17, 61. His rheumatologist, Dr. Melissa Elder M.D., who provided a very thorough history when she examined him on March 22, 2011, doubted that he had septic arthritis, but agreed with completion of the treatment for infection because an infection could not be ruled out based upon the negative arthrocentesis that was taken after he had been on antibiotic treatment. Pet. Ex. 4A at 12-13. She did exclude systemic rheumatoid arthritis from her differential. Id. She referred him to an ophthalmologist to evaluate for uveitis, stating that if he had uveitis, he has pauciarticular arthritis and not septic arthritis. Pet. Ex. 4A at 14. She reviewed his MRIs and there was no mention of enthesitis in those reports or in her evaluation. See id. at 10-14 (Dr. Rose agreed that the MRIs did not describe enthesitis. Tr. at 242). From there, the definition of the subcategory of the disease, the nature of all of the laboratory findings, and the date of onset have been the subject of disagreement between the experts. The various subcategories of JIA contain multiple criteria that seemed to eliminate L.C. from most, if not all, of those categories.

Dr. Brawer reviewed the older Park City subcategories of JIA and thought that the most similar subcategory to describe L.C. was what he called the fourth category: female patients between 1 and 3 years old, about 40% of whom had a positive ANA test and about 40% of whom develop posterior uveitis. Tr. at 58-61, 68; Pet. Ex. 19 at 5. But, as he observed, this category of JIA occurs almost exclusively in girls who are ANA positive and HLA-B27 negative. Tr. at 66. L.C., however, is HLA-B27 positive, and while he was initially ANA positive on one test during an admission at Arnold Palmer Hospital in February 2011, he was ANA negative on a subsequent test. Id.

Dr. Rose proposed that the most likely diagnosis is "enthesitis related arthritis" (ERA), which is "a term introduced in the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA)." It "is predominately a disease affecting joints of the lower extremities and, eventually, the axial skeleton, and it is characterized by the absence of autoantibodies such as rheumatoid factor (RF) and antinuclear antibodies (ANA) and by a strong association with the human leukocyte antigen B-27 (HLA-B27)." Resp. Ex. C at 2.[19] The chapter in the Textbook of Pediatric Rheumatology defining enthesitis-related arthritis indicates that this subcategory is referred to as seronegative enthesitis and arthritis syndrome (SEA), and that children with this syndrome usually initially lack the sacroiliac joint involvement that is the hallmark of juvenile ankylosing spondylitis (JAS). Id. at 4 (CASSIDY at 274). It states: "These children are seronegative (lack RF or ANA), have enthesitis (usually around the heel or knee), and have arthritis of a few small joints of the lower extremities" and the syndrome probably represents, for the most part, children with early JAS. Id. Dr. Rose favored this diagnosis, in part because of the inability to

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[18] Resp. Ex. E, David C. Wraith, Michael Goldman, & Paul-Henri Lambert, *Vaccination and Autoimmune Disease: What is the Evidence?*, THE LANCET 1(2003).

[19] Resp. Ex. C, JAMES CASSIDY ET AL., Chapter 17, TEXTBOOK OF PEDIATRIC RHEUMATOLOGY 272 (6th ed. 2011).

fit L.C. into other criteria, and because he minimally met ILAR criteria in that he had arthritis, was HLA-B27 positive, and arguably had anterior uveitis. Tr. at 158. Notably, he did not meet the criteria of sacroiliac joint tenderness, family history of confirmed disease, or onset in a boy older than eight years of age. Resp. Ex. C at 3 (CASSIDY at 273). Problematically, L.C. was ANA positive on one of two tests, had no symptoms of back pain, and was never considered to have a diagnosis of enthesitis by any of his treating physicians, had no evidence of enthesitis on any of his MRIs, and his treating rheumatologist believed that he was ANA positive despite the conflicting test results. See Pet. Ex. 4A at 13.

The experts in this case disputed whether L.C. developed uveitis several months after the onset of rheumatoid arthritis. When he was initially sent to an ophthalmologist by Dr. Elder, his treating rheumatologist, he did not have evidence of uveitis. Eventually, in November 2012, the ophthalmologist did see keratic precipitates in the left eye and diagnosed uveitis. Pet. Ex. 11 at 27. Keratic precipitates are inflammatory cellular deposits on the corneal surface. See Tr. at 75. Dr. Brawer did not believe that there was sufficient description of the keratic precipitates in the medical records to make a diagnosis of uveitis, as keratic precipitates can be caused by conditions other than uveitis such as trauma to the eye. Id. at 75-76. He did acknowledge that keratic precipitates were seen on the slit lamp exam, but stated that the doctor did not describe whether they were on the endothelial or epithelial side of the cornea and there was not fluid or debris described in the anterior chamber, nor pain or redness in the eye which would be typical symptoms of uveitis. Tr. at 75-79. The keratic precipitates seen in the left eye in November 2012 cleared with treatment, but were seen again in February 2013, this time in both eyes. Pet. Ex. 11 at 17, 21, 24. They also cleared with treatment. See id. at 12. Dr. Rose argued that ophthalmologists, or at least those who examine his JIA patients, say uveitis when they see keratic precipitates without more detailed explanation as to the location of the keratic precipitates. Tr. at 158-60, 217. He acknowledged that a corneal abrasion or other type of eye trauma can leave behind keratic precipitates just as a flare of uveitis can, but he said that in a child being referred for JIA if keratic precipitates are seen, then that is uveitis. Tr. at 159, 215-17.

While for our purposes in this Program a more detailed description of the ophthalmology findings would be helpful, I think it is likely that in a child with signs and symptoms of arthritis, and no known history of eye trauma or viral infection in the eye, it is reasonable to conclude that the presence of the keratic precipitates is enough to conclude uveitis as the treating ophthalmologist did. Accordingly, it is reasonable to conclude that the eventual presence of uveitis confirmed the diagnosis of pauciarticular arthritis and ruled out septic arthritis, even though no physician ever observed a significant red eye or heard the parents report claims of eye pain.

The significance of the debate regarding whether L.C. had uveitis appeared to be in whether L.C.'s arthritis could be subcategorized as enthesitis-related arthritis. Dr. Rose contended that with a diagnosis of acute anterior uveitis, L.C. met the minimum test for ERA JIA, as he had arthritis and HLA-B27, even though he did not have enthesitis, was probably ANA positive, and was not nearly in the right age range. Tr. at 158. Dr. Brawer, on the other hand, did not believe that L.C. had ERA. It should also be noted that the treating rheumatologist, Dr. Elder, when making a referral to ophthalmology, stated that if L.C. had uveitis, he had pauciarticular arthritis and not septic arthritis—without any mention of ERA. Pet. Ex. 4A 13.

In short, the two testifying rheumatologists spent a good deal of time and testimony essentially trying to force a round peg into a square hole. There seemed to be no subcategory that

perfectly fit the disease presentation of L.C. He was not older than 8 years old, he had no evidence of enthesitis, he was not a girl, he was HLA-B27 positive, it is not known if he will develop ankylosing spondylitis later in life, and he was ANA positive on one test and negative on another. In addition, there was disagreement between the experts as to whether or not he had uveitis. It initially appeared that the gist of the argument over JIA subtypes concerned whether one subtype fit more into an inflammatory or innate immune response or into more of an autoimmune or adaptive causal mechanism. However, I asked Dr. Rose whether the lengthy discussion of the subcategories of JIA made any difference in terms of the analysis of causation in this case, and he answered: "[I]t doesn't have that much of a bearing." Tr. at 223. Dr. Rose discussed various patients who have different presentations and stated that while 8% of the population is HLA-B27 positive most do not develop ERA or ankylosing spondylitis. He concluded by saying: "So no, I don't have any opposition to call this ERA diagnostic possibility number one, or polyarticular ANA positive, persistent variant JIA second possibility." Id. He went on to explain that "ERAs are having more of an autoinflammatory flavor these days, in ERA JIA a positive is more autoimmune, which also has implications when one part of the immune system is activated. The autoimmune diseases are more—more, but not only, acquired, or immune, and the autoinflammatories are more innate. But it's a spectrum. We're not separating them anymore now." Id. at 224. At the end of the day, Dr. Rose's explanation appeared to be a rather fair approximation of this case, as most if not all of the subcategories of JIA appeared to have at least one if not more missing elements in the presentation of L.C. He was a little boy, less than one year old, with what appeared to be a painful right knee and a flexion contracture, was HLA-B27 positive and possibly ANA positive or possibly not, with no evidence of enthesitis. It short, his signs and symptoms did not fit clearly into any one category and it seems likely that the cause of his disease did not fit clearly into one end of the spectrum or the other either.

The significance of the subcategorization of L.C.'s JIA appears to be in Dr. Rose's argument that the ERA form of the disease tended more to the autoinflammatory rather than autoimmune end of the spectrum of JIA. Dr. Brawer generally agreed that ERA was more on the inflammatory end of the spectrum, but he thought the condition was autoimmune in L.C. Neither expert in this case was an immunologist and the testimony about the immunological aspects of this case was often hard to follow and pin down. It was replete with analogies to unrelated diseases, which shed little light upon the issue before the undersigned and contained some uncertainty about the immunological mechanisms at play in JIA and in this specific presentation. Both physicians agreed that the understanding of JIA is very much evolving and far from completely understood. It seemed that the understanding of its causation in this case was complicated by the fact that L.C. for the most part did not fit clearly into one of the multiple subcategories of the disease. Dr. Rose reflected on the evolving nature of the understanding of the molecular causation that may be involved in this case when he explained that in a person who is HLA-B27 positive (which 8% of the population is) the HLA-B27 variant performs the function of antigen presentation to CD8 T cells, which function to kill the infected cells. Tr. at 169. According to Dr. Rose, the T cells then leave a trail of inflammatory triggers or free oxidants which apparently stimulate an additional inflammatory response. Id.

Dr. Rose did agree, as stated in the Textbook of Pediatric Rheumatology, that this disease is multifactorial. Tr. at 243-44 (referencing Resp. Ex. D, Chapter 13, TEXTBOOK OF PEDIATRIC RHEUMATOLOGY). He described JIA as a spectrum of disorders that have both autoimmune and autoinflammatory elements. Id. at 247. Interestingly, as Dr. Rose described the inflammatory element, it appears that the inflammatory action is secondary to the CD8 T cell response which

leaves triggers for the innate immune system behind. See Tr. at 169. As CD8 T cells are part of the adaptive immune system, it would appear that Dr. Rose is describing an immune-mediated inflammatory response. So whether the disease presentation leans toward autoimmune or autoinflammatory seems not to make much difference in terms of whether molecular mimicry secondary to a vaccination could be the causal factor, as it would generally be argued that molecular mimicry would be most likely to stimulate the B cell or T cell response of the adaptive immune system more so than a purely innate inflammatory response. In this case, Dr. Rose's explanation suggests a primary autoimmune or T cell response to an antigen, which is then followed by inflammation triggered by the T cells.

There also appears to be agreement between the parties that the thinking in rheumatology is that a combination of some genetic vulnerability, possibly HLA-B27, and some environmental factor combine at a vulnerable time to cause the onset of rheumatoid arthritis. On cross-examination, Dr. Rose agreed that environmental factors play a role in the development of JIA. Tr. at 254-56. As reviewed on cross-examination, Dr. Rose submitted literature that also indicates that the ultimate presentation or phenotype of JIA, assuming it develops, is likely to differ based upon the child's age of vulnerability. Id. at 256-57. The literature also said that environmental factors, of which Dr. Rose observed there could be many, include infection as the most likely, and that microbial antigens can induce cross-reactive immune responses against self-antigens, whereas infections can non-specifically enhance their presentation to the immune system. Resp. Ex. E (Wraith at 1). Dr. Rose agreed, and also agreed that DTaP is a type of microbial antigen "[a]s much as the ear infection." Id. at 258. In fact, it should be observed that both DTaP and ear infections present multiple antigens to the immune system.

While Dr. Brawer observed that there could be multiple mechanisms that give rise to autoimmune diseases, including JIA, and did not want to be fully committed to one mechanism, he did assert on cross-examination that his lead mechanism was molecular mimicry as there were likely cross-reacting antigens in the vaccine that could cross-react with self-antigens in a manner similar to what has been shown with some infectious antigens. Tr. at 144-45. He acknowledged that he was not an immunologist and had not studied the specific potential homologies between DTaP and self- antigens that could be involved in JIA. Id. at 145. However, he supported his argument by presentation of several articles from the medical literature. In particular, an article by Sutjita et al.[20] showed that cross-reactive epitopes occur on routinely used toxoid vaccines and self-antigens. The authors noted that it was easier to imagine cross-reactivity with an infectious organism with multiple epitopes, but found that even in purified proteins as in tetanus and diphtheria toxoids, the exposure to the immune system of multiple cross-reactive epitopes was likely. They demonstrated that tetanus toxoid carries at least 20 distinct epitopes aside from the intended ones. Pet. Ex. 21 at 5 (Sutjita at 195). Dr. Brawer also submitted an article by Kanduc[21] demonstrating broad cross-reactivity to the HPV vaccine, which demonstrated at least 60 potential

[20] Pet. Ex. 21, Sutjita et al., *Polyspecific Human and Murine Antibodies to Diphtheria and Tetanus Toxoids and Phospholipids*, 73 CLIN. EXPERIMENTAL IMMUNOLOGY 191 (1988).

[21] Pet. Ex. 22, Darja Kanduc, *Quantifying the Possible Cross-Reactivity Risk of the HPV16 Vaccine*, 8 JOURNAL OF EXPERIMENTAL THERAPEUTICS AND ONCOLOGY 65 (2009).

cross-reactivities to HPV 16. Further, he submitted a review article by Vial,[22] which discussed multiple vaccines and autoimmune disease. Vial specifically suggested that the presence of HLA-B27 in many rheumatoid arthritis patients suggests a possible vulnerability to vaccines in these patients. Pet. Ex. 23 at 4 (Vial at 88).

Dr. Rose agreed that molecular mimicry is an active concept in autoimmunity theory that has been published for years and continues to be. Tr. at 265-66. He agreed that it should be included in any review of autoimmunity, and that it has been proven in some diseases. Id. However, he said that there was not enough evidence presented to him that L.C.'s disease was the result of mimicry with a tetanus toxoid. Id. at 266-67. In order to conclude that L.C.'s JIA was the result of molecular mimicry with tetanus or diphtheria toxoid, Dr. Rose said he would like to see an innate response to the vaccine like fever, and research that demonstrated in an animal model the development of arthritis or uveitis after the injection of an equivalent vaccine. Id. at 267-68. He said that a study of identical twins done in Cincinnati has shown a genetic propensity for JIA, but also agreed that even in twins with identical genes just because one developed JIA did not mean that the other would. Id. at 269-70. He acknowledged that he was not aware of any other studies done specific to the issue in this case. He did state that he thought that infection occurring almost concomitantly with what he thought was the onset of the JIA symptoms was a more likely cause than a vaccine administered seven weeks prior to vaccination. Id. at 272.

This brings the discussion to the question of the onset of the disease, which was discussed at length by Mrs. Cabrera and the two doctors, and was demonstrated by videotapes taken with Mrs. Cabrera's cell phone of the child before the vaccination, in September (one month after the vaccination), and again at Christmas time. Mrs. Cabrera testified that two videos showed L.C. before the vaccination. One showed him bouncing on both legs while in a bouncy chair on August 6, 2010. Pet. Ex. 46. The other showed him weight bearing on both legs while being held by his mother in the surf at the beach on August 21, 2010. Pet. Ex. 49. Both doctors agreed that he appeared perfectly normal in these videos, and there was little question that he looked normal and bore weight on both legs on review of the film. See Tr. at 289.

L.C. received the DTaP vaccination on August 30, 2010. The third video, dated September 29, 2010, was taken just under a month after the vaccination. Pet. Ex. 47; Tr. at 25. This video was the subject of controversy. It showed baby L.C. crawling across the room to get to a toy. He initially appeared to assume a normal crawling position with both hands and both knees down. But then, almost immediately, he extended the right leg out to the side with the knee in the air while both hands and the left knee were on the ground. He crawled across the room with the right leg extended in this manner with only his toes touching the floor. Mrs. Cabrera testified that when he started to crawl during the month of September, "he had his left knee on the ground like normal, but his right leg completely out to the side." Tr. at 7. "He never put the right knee on the ground." Id. Initially L.C.'s parents did not think anything of it and called it his "crab crawl." Id. at 8. A final video was taken on Christmas Day, 2010. Pet. Ex. 50. Mrs. Cabrera described that he had been crawling with the right leg extended out to the side for three months at this point, and that was demonstrated in the Christmas video as well. Tr. at 26.

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[22] Pet. Ex. 23, Thierry Vial & Jacques Descotes, *Autoimmune Diseases and Vaccinations*, 14 EUR. JOURNAL OF DERMATOLOGY 86 (2004).

The discussion of the videos is particularly important because L.C. had an ear infection and a case of the flu in late October. He was completely healthy between the time of the vaccination and the time the September 29, 2010, videotape was recorded. Dr. Brawer described the September 29 video as demonstrating pain protective behavior, with the child assuming an abnormal crawling position as readily demonstrated on the film. Tr. at 312. L.C.'s mother testified that he continued to crawl in this manner until after he received treatment for rheumatoid arthritis. Id. at 16. Dr. Rose, on the other hand, testified that what was shown on the video was not pain protective but was rather normal early crawling. Tr. at 201. Dr. Rose said that in babies who are not yet speaking a flexion contracture is the most specific physical finding on examination. Id. at 202-03. Dr. Rose looked at the video and freeze framed it at second 18. Id. at 205. He said that what he saw at second 18 was a full extension of the right leg, which L.C. would not be able to do if he had a flexion contracture. Id. at 206. Dr. Brawer strongly disagreed with this conclusion, saying that the leg was not fully extended and there was a 20 degree contracture in the frame at second 18. Id. at 312. The final video, on Christmas Day, showed L.C. crawling in what appeared to be the very same manner as he was on September 29, but in the Christmas video Dr. Rose agreed that he clearly had a flexion contracture at that time and certainly had arthritis. Tr. at 292.

Because of the importance of this issue, I carefully studied the video tapes and the mother's testimony. When watching the September and December videos it certainly appeared that the baby was crawling in the same manner in both. He had an asymmetrical leg extension on the right in both. His mother testified that he always crawled in this manner from the time that he started crawling in September until he was treated for JIA. If this unusual crawling actually constituted normal early crawling behavior in a child who was just learning, it is highly likely that he would have outgrown it in this time, and it is most unlikely that it would have always been asymmetric on the right. If this were normal early crawling behavior in September it seems unlikely that the same crawl would be explained by arthritis in December.

Most importantly, however, I focused on the second 18 freeze frame that Dr. Rose emphasized. The view of the child is from the head front position, so if the viewer focuses on the extended right leg at second 18, it is difficult to tell if the leg is flexed or fully extended. However, there is a very distinct shadow of the leg on the carpet beneath the right leg. By looking at the shadow it is completely clear that the leg was not fully extended and that there is approximately a 20 degree flexion at the knee, as Dr. Brawer testified. Thus, onset in September cannot be ruled out by a fully extended right leg in the video. Dr. Rose emphasized that a flexion contracture, in which the knee cannot be extended, is the best diagnostic tool. But this does not mean that the elevation and the contracture were not secondary to pain. It appears likely that the child developed this crawling posture as a means of avoiding pain when his right knee came in contact with the floor. The likely knee pain became more evident to his parents when he cried in response to their attempts to extend the leg while changing his diaper during October. It should also be noted that Dr. Franz, L.C.'s pediatrician, recorded on October 26, 2010, that L.C.'s father said L.C. would not bear weight on his right leg and crawled funny, and on October 29, Dr. Franz noted that L.C. wouldn't bear weight on his right leg for 2 weeks. Thus, Dr. Franz' notes refer to the onset of L.C.'s difficulty bearing weight beginning before the late October otitis media and flu infection.

Accordingly, I have concluded that consistent with Mrs. Cabrera's testimony and the evidence shown on the video tape, the onset of the child's rheumatoid address was in late September 2010, not in late October. Therefore, the otitis media and influenza the baby had in late October more likely than not had no causal role in the onset of his arthritis.

V. CONCLUSION

Both experts agree that L.C. developed juvenile idiopathic arthritis at about nine months of age. He received his first DTaP vaccination on August 30, 2010. I have concluded that he was showing signs of pain protective behavior in his crawl at the time of a video of him crawling on September 29, 2010. His mother testified that he crawled with his right knee raised and leg extended since he began crawling about a week before and continued to crawl in that manner until after he was treated for JIA. When he began to stand, he was not weight bearing on the right leg. Therefore, I have concluded that the onset of the disease was in September, at which time there had been no potentially causal alternative illnesses intervening between the vaccine and the date of onset about three weeks later. He was diagnosed with JIA and uveitis. The condition developed and L.C. demonstrated an obvious flexion contracture in the December video as both experts agreed. The crawling posture did not change until after he had treatment for juvenile rheumatoid arthritis.

Dr. Brawer argued that there could be multiple mechanisms for the instigation of JIA secondary to a vaccination but settled on molecular mimicry as the most likely mechanism. He supported this opinion with an article by Sutjita et al., which found that even a purified tetanus or diphtheria antigen used in vaccines had at least 20 epitopes for antigens other than the intended ones. He argued that there was likely mimicry between the vaccines and the phospholipids in the synovial fluid. He opined that the onset of the disease was in September and that there was no other reasonable explanation for the triggering of the disease in this child. A three-week onset for an adaptive immune response to the vaccine with a secondary inflammatory response is reasonable.

Both parties agreed that the causation of JIA is multifactorial. The general thinking appears to be that an inherent vulnerability, at an appropriate developmental interval, combines with an environmental trigger to cause JIA. Dr. Brawer offered the opinion that by the mechanism of molecular mimicry, the DTaP vaccine was most likely to be the environmental trigger in this case. Dr. Rose was not comfortable that a particular environmental trigger could be said to be the "but for" factor, although he was willing to attribute potential causation by mimicry to the ear infection and flu that the child suffered shortly before the first visit to an orthopedist in November.

Dr. Rose's opinion was based on his assertion that the onset did not occur until after L.C. suffered several episodes of otitis media and the flu at the end of October, 2010, and his feeling that he would want to have animal testing to prove the molecular mimicry between the vaccine and the joints involved in JIA. While it would be wonderful to have the type of proof that Dr. Rose found necessary, the law of this Program does not require that level of certainty. Althen requires a reasonable theory, a logical cause and effect, and acceptable timing. While the petitioners' evidence on the mechanism of molecular mimicry could have been stronger, the mechanism and support for it was sufficient for it to be a reasonable mechanism that can explain the onset of an autoimmune disease such as occurred in this case. The manner in which the disease developed fit logically with the explanation of molecular mimicry between the vaccine and the synovial fluid in the L.C.'s right knee and the timing was acceptable. Petitioners are entitled to compensation.

IT IS SO ORDERED.

s/Thomas L. Gowen

Thomas L. Gowen
Special Master