In the United States Court of Federal Claims

No. 08-284V
(Filed under seal June 30, 2017)
(Reissued July 26, 2017)†

T.M. and R.R.M., parents and natural guardians of A.P.M., a minor,	Vaccine Act; off-table case; DTaP vaccination; autism spectrum disorder; cerebral folate deficiency; folate receptor blocking autoantibodies; *Althen*; molecular mimicry; medical condition not demonstrated; unreliable theory; causation not established; medically-acceptable temporal relationship not explained.
Petitioners,	
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	

Robert J. Krakow, New York, N.Y., for the petitioners.

Lynn E. Ricciardella, Torts Branch, Civil Division, U.S. Department of Justice, with whom were *Benjamin C. Mizer*, Principal Deputy Assistant Attorney General, *C. Salvatore D'Alessio*, Acting Director, *Catharine E. Reeves*, Acting Deputy Director, and *Heather L. Pearlman*, Assistant Director, all of Washington, D.C., for the respondent.

OPINION AND ORDER

WOLSKI, Judge.

Petitioners, [T.M. and R.R.M.], have moved for review of Special Master Brian H. Corcoran's decision that they are not entitled to compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §§ 300aa-10—300aa-15 (Vaccine Act or Act). Petitioners assert that the Diptheria Tetanus acellular

† Pursuant to Vaccine Rule 18(b) of the Rules of the United States Court of Federal Claims, this opinion was initially filed under seal. At petitioners' request, their names have been replaced with their initials, placed within brackets. The opinion is now reissued for publication with some minor, non-substantive corrections.

Pertussis (DTaP) vaccine administered to their son, A.P.M., on July 14, 2006, triggered a form of cerebral folate deficiency which caused A.P.M.'s autistic regression, ultimately resulting in apraxia of speech and Autism Spectrum Disorder (ASD) features. Corrected Pet'rs' Mot. for Review (Mot.) at 4; Third Am. Pet. (Pet.) ¶¶ 14–19, 21–22. The Special Master denied compensation in this off-table case, finding that petitioners did not establish that A.P.M. suffered from cerebral folate deficiency and failed to satisfy any of the prongs articulated in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). Decision at 31–44. Petitioners contend that this decision was arbitrary in several respects. Mot. at 1–2, 19–30. For the reasons that follow, the Court **DENIES** petitioners' motion and **SUSTAINS** the decision of the Special Master.

I. BACKGROUND[1]

A. The Vaccinations, Medical History, and Diagnosis

Petitioners' son, A.P.M., was born on April 16, 2005, after a relatively normal pregnancy with few complications. *See* Pet'rs' Ex. 2. Throughout his first months, A.P.M. had several well-child visits with his pediatrician, Dr. Rick A. Kooima. He received the vaccinations for *Haemophilus influenzae* type B ("Hib") and pneumonia, as well as the Pediarix vaccination (for diphtheria, tetanus, pertussis, hepatitis B virus, and poliomyelitis), at his two-, four-, and six-month visits, and was noted to be developing well. Pet'rs' Ex. 20 at 8; Pet'rs' Ex. 1 at 1, 12–14, 16, 41–44; Pet'rs' Ex. 34 at 10; Pet'rs' Ex. 63 at 3. His mother, however, noted that A.P.M. was "ill and irritable" and had signs of severe discomfort following the first two administrations of the Hib and Pediarix vaccinations, Pet'rs' Ex. 63, ¶¶ 4–5, although the medical records do not reflect any additional treatment due to these reactions, *see* Pet'rs' Ex. 1 at 14 (noting mother's report that A.P.M. was "ill for about a month" following the first shots, and "was fussy and more irritable").

After being concerned with A.P.M.'s reactions to the initial vaccinations, [T.M. and R.R.M.] asked Dr. Kooima to defer additional immunizations at the 12-month well-child visit. Pet'rs' Ex. 1 at 11, 40. Petitioners did not want A.P.M. to receive the varicella vaccine, but agreed that he could receive the Prevnar vaccination (for pneumonia) at the next well-child visit. *Id.* Before A.P.M.'s 15-month well-child visit, [T.M. and R.R.M.] brought A.P.M. back to see Dr. Kooima because of their concern that he was breaking into a rash whenever his skin encountered a milk-based product. Pet'rs' Ex. 1 at 9, 48. Doctor Kooima tested A.P.M. for allergies, but all testing was negative, and he instead diagnosed A.P.M. with rhinitis/conjunctivitis. *Id.* At this time, A.P.M. was noted to be "well-developed." *Id.*

[1] The background facts are primarily drawn from the Special Master's opinion, with any relevant disputes concerning these facts specifically noted.

During his 15-month well-child visit on July 14, 2006, A.P.M. received the combination DTaP and Hib vaccine and the measles, mumps and rubella ("MMR") vaccine. Pet'rs' Ex 1 at 1, 16, 38; Pet'rs' Ex. 63 at 3; Pet'rs' Ex. 34 at 10. The medical records from Dr. Kooima's office reflect three phone calls from petitioners between the date of the vaccinations and A.P.M.'s 18-month visit. Pet'rs' Ex. 1 at 8. Five days after the vaccinations, [T.M.] called concerning a yeast infection. *Id.* On July 24, 2006, ten days after the vaccinations, she called to report that A.P.M. had a low-grade temperature and rash. *Id.* Twenty days later, [T.M.] called about A.P.M.'s watery eyes and congestion. *Id.*

The record from A.P.M.'s 18-month well-child visit, made on October 18, 2006, noted that A.P.M. was very healthy, that his diet included eight to ten ounces of whole milk, and that petitioners were "concerned" about his "talking." Pet'rs' Ex. 1 at 37. The contemporaneous records include no additional reports or details regarding this concern, until A.P.M.'s 2-year well-child exam. *See id.* at 7–8. On April 17, 2007, petitioners reported to Dr. Kooima that A.P.M. "was saying around a dozen words when he was 18 months old," but had stopped saying them and learned no new ones. *Id.* at 7. His tendency "to walk on his toes and flap his hands" was also noted. *Id.* Due to his concerns, Dr. Kooima referred A.P.M. to a speech therapist and to Dr. Jerome Blake, a developmental pediatrician. *Id.*

The following month, on May 10, 2007, petitioners brought A.P.M. to Dr. Blake's office, where he was evaluated by Rebecca Mork, a certified nurse practitioner. *See* Pet'rs' Ex. 7 at 18–24. Petitioners reported that A.P.M. had been using "approximately 6–10 words" but lost skills between the age of 18 and 20 months, and retained just one of those words. *Id.* at 18. He was then using one to three words, *id.*, and it was noted that he "was using simple words between 15 and 17 months," *id.* at 20. Over the next six months, as A.P.M. was brought back to that office and also met with various therapists and specialists, the records of petitioners' reports of the time period in which A.P.M. lost his language skills varied somewhat. On May 23, 2007, [T.M.] reported that A.P.M. lost skills at "around 19 months of age." Pet'rs' Ex. 8 at 11. The following month, an occupational therapist was told that A.P.M. "used single words at 15-17 months," and then regressed "[o]ver a period of two months." *Id.* at 6. In October, Ms. Mork was informed that A.P.M.'s loss of language skills occurred between the ages of 18 months and 2 years. Pet'rs' Ex. 7 at 9. And on November 8, 2007, petitioners told a special education specialist that A.P.M. "had 15-20 word approximations before" receiving the vaccinations at 15 months of age, then "started to regress and . . . eventually lost all of his language and skills listed between 15-18 months." Pet'rs' Ex. 12 at 6.

In a declaration filed on June 15, 2015, [T.M.] stated that "A.P.M. was using as many as 20-30 words until shortly after July 14, 2006, although many of his words were garbled and difficult to understand," and that "approximately" from the time he was 16 months old through 20 months old, he "stopped using many of the words" and was reduced to just one word approximation. Pet'rs' Ex. 63 ¶¶10, 13.

She stated that "[w]ithin weeks" of receiving the 15-month vaccinations, A.P.M. had begun to lose some of the words he had been using, *id.* ¶ 9, and became socially withdrawn and stopped playing with his toys, *id.* ¶¶ 11–12. At the hearing, she testified that within three to three and one-half weeks after he received the vaccinations, she noticed that A.P.M. was "interacting less" and "talking less," and that by Christmas he was using just one word. Hearing Tr. (Tr.) at 22–23. She also stated that the medical records from Dr. Kooima's office did not reflect the concerns about A.P.M.'s apparent regression in the three month period following the vaccinations in part because [R.R.M.] at that time did not agree that A.P.M. was exhibiting any problems, and she suggested that it was possible that phone conversations with nurses went unreported. Tr. at 27–29, 71–72.

On November 8, 2007, A.P.M. was first diagnosed with "autistic disorder" because he exhibited many characteristics of an ASD, including expressive and receptive language delay. Pet'rs' Ex. 7 at 27–29; *see also* Pet'rs' Ex. 13 at 19. The psychologist, Dr. Tracy Stephens, drew this conclusion from A.P.M.'s score of 32.0 on the childhood autism rating scale, which indicated that he had "mild to moderate" autism. Pet'rs' Ex. 7 at 27–29. On this same day, A.P.M. also saw Alison Kringstad, a special education specialist at Behavior Care Specialists, who confirmed A.P.M.'s autism diagnosis using the nine criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Pet'rs' Ex. 12 at 6–9.

In 2010, A.P.M. began to be treated by Dr. Richard Frye, a child neurologist at the University of Texas. Pet'rs' Ex. 16 at 52. At Dr. Frye's direction, A.P.M.'s blood was tested for the presence of folate receptor blocking and binding autoantibodies. Pet'rs' Ex. 16 at 38–39. The results, reported on October 23, 2010, showed that A.P.M. had a folate receptor blocking autoantibody titer of 1.19 picomoles per milliliter (pmoles/ml), which was considered high since the titer exceeded 1.0 pmoles/ml.[2] *Id.* at 38. After reviewing the results with [T.M.], Dr. Frye expressed the opinion that the blocking autoantibodies were "in the high range and significant," although the titer value was misstated in the written record as 1.9 pmoles/ml. *Id.* at 35. Doctor Frye noted that such antibodies were "seen in children with cerebral folate disorder." *Id.* He acknowledged this was a "severe disorder," resulting in blindness and "other very striking neurological features that are not seen in [A.P.M.]," but suggested it was "very possible" that A.P.M. suffered from "a mild form of this disease." *Id.*

Cerebral folate deficiency is "associated with low levels of 5-methyltetrahydrofolate (5MTHF), the active folate metabolite in the cerebrospinal fluid," compared to normal folate levels in the blood and elsewhere. Vincent T.

[2] This measurement was based on a range dependent on levels found for "normal population, women with neural tube defect and children with [cerebral folate deficiency] syndrome. Pet'rs' Ex. 16 at 38.

Ramaekers, et al., *Autoantibodies to Folate Receptors in the Cerebral Folate Deficiency Syndrome*, 352 (19) N. Engl. J. Med. 1985, 1985 (May 12, 2005) (Pet'rs' Ex. 50, Ref. 1) (Ramaekers I). Accordingly, Dr. Frye ordered a lumbar puncture, or spinal tap, to measure the level of folate in A.P.M.'s cerebrospinal fluid (CSF), which was performed on March 30, 2011. Pet'rs' Ex. 16 at 10–11, 35.[3] The results showed the amount of 5MTHF in A.P.M.'s cerebrospinal fluid to be 53 nanomoles per liter (nmol/L), an amount characterized as "within our reference range" of 40 to 128 nmol/L, and therefore normal. Pet'rs' Ex. 16 at 22. In a September 2011 record generated after a discussion with petitioners, Dr. Frye characterized the measured folate level as "low normal," *id.* at 3, but in a February 2014 record he described the level as "frank below-normal" in noting that A.P.M. "has been diagnosed with cerebral folate deficiency." Pet'rs' Ex. 46 at 1.

B. The Petition and Hearing Before the Special Master

Petitioners filed this vaccine petition against the Secretary of Health and Human Services (Secretary or respondent) on April 17, 2008, as a short-form autism petition to be included in the Omnibus Autism Proceeding ("OAP"). *See* Petition at 1. After the conclusion of the OAP test cases in 2010, Petitioners opted to continue pursuit of their claims, and filed an amended petition on May 14, 2012, alleging that A.P.M.'s receipt of the MMR and/or the DTaP-Hib vaccines in July 2006 had caused his regressions. Am. Pet. ¶¶ 16–23. On October 4, 2012, a second amended petition was filed, adding additional details including a rechallenge theory of causation. *See* Second Am. Pet. ¶ 22. On June 16, 2015, the petitioners again amended their petition to conform their claim to the proof petitioners anticipated would be offered at the evidentiary hearing. *See* Third Am. Pet. (Pet.) ¶¶ 3–4.[4]

An entitlement hearing was held in Washington, D.C., on July 28 and 29, 2015. *See* Tr. In addition to [T.M.], noted above, each party's expert testified during the hearing.

Petitioners' expert was Dr. Yuval Shafrir, a pediatric neurologist who is affiliated with Sinai Hospital in Baltimore. Tr. at 91. He submitted both an expert report, Pet'rs' Ex. 50, and a supplemental expert report in response to respondent's expert report, Pet'rs' Ex. 53. He graduated from the Sackler School of Medicine at Tel Aviv University in 1982, and thereafter did residencies in pediatrics at Kaplan University and the Bellinson Medical Center in Israel. Pet'r's Ext. 62 at 1. Doctor Shafrir then completed residencies in pediatrics at North Shore University Hospital

[3] A Magnetic Resonance Imaging (MRI) examination of A.P.M.'s brain was also ordered and performed at that time, showing normal results. Pet'rs' Ex. 16 at 47–50.

[4] The rechallenge theory of causation was dropped from this final version of the petition.

in New York, and in pediatric neurology at the Washington University Medical Center in Missouri. *Id.* at 1–2; Tr. at 88. He is currently licensed to practice medicine in Maryland, and has board certifications in child neurology, although he has not renewed his board certification in pediatrics. Tr. at 88. Doctor Shafrir has worked and taught in the areas of pediatrics and neurology across the country, and currently teaches at the University of Maryland School of Medicine. Pet'rs' Ex. 62 at 3–4. He has also written extensively on issues of pediatric neurology. *Id.* at 4–6; Tr. at 89-90. He estimated that he had treated 1500 patients with autism. Tr. at 91. Doctor Shafrir testified as an expert in pediatric neurology. Tr. at 94.

Respondent's expert was Dr. Max Wiznitzer, a clinical physician at Rainbow Babies and Children's Hospital in Cleveland and a professor of pediatrics and neurology at Case Western Reserve University. Tr. at 239–40; *see* Resp't's Ex. B at 1. Doctor Wiznitzer graduated from Northwestern University with a bachelor's of science in medicine in 1975 and a medical degree in 1977. Tr. at 236. He then completed a three-year internship and residency in pediatrics at Cincinnati Children's Hospital, followed by a one-year fellowship in child development and developmental disorders at the Cincinnati Center for Developmental Disorders. *Id.* He also completed a three-year child neurology fellowship at the University of Pennsylvania and Children's Hospital of Philadelphia, followed by a two-year National Institute of Health fellowship in disorders of higher cortical function in children at the Albert Einstein College of Medicine in the Bronx, New York (which involved working with children with autism spectrum disorders). *Id.* Doctor Wiznitzer also serves as a journal reviewer and on two editorial boards (the Lancet Neurology and the Journal of Child Neurology). *Id.* at 245–46. He holds board certifications in pediatrics, neurology (with special qualification in child neurology), and neurodevelopmental disabilities. *Id.* at 237–40.

At the time of the hearing, Dr. Wiznitzer estimated that over a quarter of the patients that he treated in his clinical practice may have been diagnosed with autism. Tr. 238. He has been actively involved in ASD-related research, with approximately 60 publications in his name, as well as teaching experience on the topic. *Id.* at 239–41. He testified as an expert in neurology, with a special qualification in child neurology. *Id.* at 247–48.

In addition to testifying to the course of A.P.M.'s symptoms, [T.M.] stated that cow's milk was introduced into A.P.M.'s diet shortly before he was 18 months old, but was removed shortly afterwards due to concerns he might have milk allergies. Tr. at 73, 83–85. She also stated that A.P.M. continued to be fed food containing dairy products until July of 2007, after which time "his aggression lessened a bit." Tr. at 47–48; *see also id* at 86.

Petitioners' expert opined that the DTaP vaccination administered to A.P.M. on July 14, 2006, resulted in the generation of autoantibodies that block the folate receptor, ultimately causing A.P.M.'s autistic regression. *See, e.g.*, Tr. at 95, 140,

160–61, 184–85, 468. He based this on the existence of a five amino acid sequence occurring in both human folate receptor protein and in a pertussis vaccination protein. Tr. at 161–68, 224–25, 443–44, 468; *see also* Pet'rs' Ex. 53, Ref. 6 at 2. While Dr. Shafrir conceded that A.P.M. did not suffer from the severe "abnormalities" that would meet the clinical criteria for cerebral folate deficiency, Tr. at 114, 189, 204, he posited a novel syndrome, characterized by the elevated level of anti-folic receptor antibodies, which "hasn't been delineated yet" *id.* at 161, 229–30, and which may impair the brain by reducing folate in the CSF or by some other, unknown means, *id.* at 460, 468. He also expressed his belief that A.P.M.'s folate levels were lower than determined by the spinal tap, due to the possibility that blood contaminated the CSF and increased the folate level measured. Tr. at 133–34, 203–04, 449–51. As to timing, Dr. Shafrir could not "pinpoint a date or a week" for the onset of A.P.M.'s problems, but believed they arose prior to A.P.M.'s 18-months well-child visit. Tr. at 101–02, 194.

Respondent's expert was also of the opinion that A.P.M. did not have a cerebral folate deficiency, based on the latter's clinical picture and the level of folate in the CSF. Tr. at 249, 287–88. Doctor Wiznitzer did not believe that the laboratory performing the CSF analysis would have used blood-tainted fluid, and thought that any red blood cells would have been separated from the fluid before testing. Tr. at 283–84, 368–73, 436–39. He contended that a five amino acid sequence was not long enough to induce molecular mimicry, Tr. at 269–72, and noted that there was much greater homology with, and exposure to, milk. Tr. at 313–18. Doctor Wiznitzer also disputed the notion that the presence of anti-folate receptor antibodies alone could cause problems, explaining that they accomplished this by reducing folate in the CSF and the brain to low levels --- which was not the case for A.P.M. Tr. at 348, 429.

C. The Special Master's Decision and the Motion for Review

On August 9, 2016, Special Master Corcoran issued a decision denying petitioners' claim and finding that petitioners were not entitled to compensation because the record did not support their contention that the DTaP-Hib vaccine had any connection to A.P.M's developmental regression and ASD diagnosis. Decision at 44. The Special Master further found that the petitioners did not establish that the vaccine could, in fact, cause A.P.M.'s injury in the manner proposed by their theory. *Id.*

The Special Master first found that the petitioners did not establish that A.P.M. suffered from any form of cerebral folate deficiency. Decision at 31–36. The diagnosis of Dr. Frye was rejected, as A.P.M. was found to have neither the severe symptoms of cerebral folate deficiency nor low levels of folate in his CSF. *Id.* at 32-33. The Special Master rejected petitioners' argument that the spinal fluid sample was contaminated by red blood cells, finding respondent's expert's testimony more persuasive on the point and concluding that A.P.M.'s folate test results were

reliable. *Id.* He was not persuaded that low-normal folate levels in CSF were of any significance, or that Dr. Shafrir's proposed syndrome based on the mere presence of blocking autoantibodies could establish a cerebral folate deficiency. *Id.* at 33–35. The Special Master also doubted that a test for antibodies performed four years after a vaccination could be probative of the response to that vaccination. *Id.* at 36.

The Special Master next discussed a weakness he detected in petitioners' theory that the folate receptor blocking autoantibodies were generated through molecular mimicry due to a five-peptide sequence in both the DTaP vaccination and the folate receptor. Decision at 36–38. He noted that petitioners could not adequately explain why the much greater similarity between the proteins of cow's milk and the folate receptor would not also cause this autoimmune reaction. *Id.*

Although he believed that petitioners' failure to prove the existence of some form of cerebral folate deficiency was fatal to their claim, he nevertheless analyzed their causation theory under *Althen*. Decision at 38. Under the first prong, he found that petitioners failed to establish a reliable and plausible causation theory, due to their expert's limited experience with cerebral folate deficiencies; the absence of a proven link between DTaP and the blocking autoantibodies; the lack of cerebral folate deficiency symptoms; and the inconsistency between their positions on the homology between the folate receptor proteins and those of cow's milk and the DTaP vaccination. *Id.* at 38–41. The Special Master next found that "the record does not establish that A.P.M. experienced a reaction to the vaccine sufficient to suggest he was undergoing an autoimmune process." *Id.* at 41–42. And finally, he found that petitioners failed to demonstrate a medically appropriate timeframe for the alleged vaccine injury to have occurred, neither explaining "how long the production of the blocking autoantibodies would be expected to take," nor how long it would take reduced folate levels to cause development regression. *Id.* at 43–44.

Petitioners moved for review of the Special Master's decision, challenging as arbitrary his findings concerning whether A.P.M. suffered a form of cerebral folate deficiency; whether cow's milk could generate folate receptor blocking antibodies; and that petitioners failed to satisfy the *Althen* prongs. Mot. at 1–2. The Secretary filed a response, defending the decision. Resp't's Mem. in Resp. to Pet'rs' Mot. for Review (Resp't's Br.) at 11–20. The Court held oral argument on the motion, and bases this opinion on a careful consideration of the arguments of counsel, the hearing transcript, the decision below, the briefs and the pertinent medical records and literature.

II. DISCUSSION

A. Legal Standards

1. The Court's Standard of Review of a Special Master's Decision

Under the Vaccine Act, a special master must award compensation if, "on the record as a whole," he finds "that the petitioner has demonstrated by a preponderance of the evidence" the claims of the petition. 42 U.S.C. § 300aa-13(a)(1)(A) (2012). By this same standard, a special master must find that nothing else is responsible for causing the injury. *Id.* § 300aa-13(a)(1)(B). "The special master or court may not make such a finding based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion." *Id.* § 300aa-13(a)(1). A special master must consider all the "relevant medical and scientific evidence contained in the record," including any "diagnosis, conclusion, medical judgment, or autopsy . . . regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death" and "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." *Id.* § 300aa-13(b)(1). The Act further specifies that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court." *Id.* A special master is entrusted with evaluating the "weight to be afforded to any" of these sources of information. *Id.* A special master's "assessments of the credibility of the witnesses" are "virtually unchallengeable on appeal." *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000). This deference rests on the special master's "broad discretion in determining credibility because he saw the witnesses and heard the testimony," *Bradley v. Sec'y of Dep't of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993), and extends to assessments of expert testimony. *See Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325–26 (Fed. Cir. 2010).

Medical records "warrant consideration as trustworthy evidence." *Cucuras v. Sec'y of Dep't of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). These records
are "generally contemporaneous to the medical events," and "accuracy has an extra premium" because a patient's proper treatment is "hanging in the balance." *Id.* Moreover, because medical records are contemporaneous documentary evidence, conflicting oral testimony "deserves little weight." *Id.* (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947)).

In reviewing a special master's decision, our court may "set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law." 42 U.S.C. § 300aa-12(e)(2)(B) (2012). Findings of fact are to be reviewed under the "arbitrary and capricious" standard; legal questions are to be reviewed under the "not in accordance with law"

standard; and an abuse of discretion standard is used for discretionary rulings. *See Munn v. Sec'y of Dep't of Health & Human Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992). With respect to the arbitrary and capricious review standard, "no uniform definition of this standard has emerged," but it is "a highly deferential standard of review" such that "[i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines ex rel. Sevier v. Sec'y of Dep't of Health & Human Servs.*, 940 F.2d 1518, 1527–28 (Fed. Cir. 1991).

2. The Standard of Causation in Vaccine Cases

A special master may award compensation through an "off-table" or "causation-in-fact" case. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation-in-fact --- the basis for the legal entitlement to compensation when a petitioner's injury is either not listed in the Vaccine Injury Table or did not occur within the time period set forth in the Table --- must be proven under two formulations adopted by the Federal Circuit. *See Pafford*, 451 F.3d at 1355. Petitioners must establish that the vaccine was both a "but-for" cause of the injury and a substantial factor in causing the injury. *See Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). And under a three-part test articulated by the Circuit, petitioners must prove "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).[5] Petitioners bear the burden of proving causation by preponderant evidence. *See* 42 U.S.C. § 300aa-13(a)(1)(A).

A petitioner must show more than a proximate temporal relationship between the vaccination and the injury to meet his burden of showing actual causation. *Althen*, 418 F.3d at 1278; *see also Grant v. Sec'y of Dep't of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Furthermore, "[t]here may well be a circumstance where it is found that a vaccine *can* cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1327 (Fed. Cir. 2006). A petitioner could meet the first and third prongs of the *Althen* test without "satisfying the second prong when medical records and medical opinions do not suggest that the vaccine caused the injury, or where the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant

[5] Although the Federal Circuit has described the *Althen* test as an "alternative," the very same opinion makes plain that the *Althen* "prongs must cumulatively show" that the *Shyface* standard is met. *See Pafford*, 451 F.3d at 1355.

evidence." *Id*. The sequence only has to be "'logical' and legally probable, not medically or scientifically certain," and thus can be established by "epidemiological evidence and [a] clinical picture," even "without detailed medical and scientific exposition on the biological mechanisms." *Knudsen v. Sec'y of Dep't of Health & Human Servs.*, 35 F.3d 543, 548–49 (Fed. Cir. 1994). Nonetheless, the Federal Circuit has stated that while "epidemiological studies are probative medical evidence relevant to causation," they are not necessarily dispositive. *Grant*, 956 F.2d at 1149.

"The government . . . is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case[-]in-chief." *de Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1353 (Fed. Cir. 2008). If a petitioner satisfies his burden, he is entitled to compensation "unless the [government] shows, also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine." *Althen*, 418 F.3d at 1278 (quoting *Knudsen*, 35 F.3d at 547) (alteration in original).

B. Analysis

Petitioners allege that a DTaP vaccination caused their son, A.P.M., to develop an autoimmune condition that led to an autistic regression, eventually manifesting as apraxia of speech and the features of autism spectrum disorder. Mot. at 4. The petitioners raise what they style as six separate objections, which relate to the special master's findings that A.P.M. does not have any form of cerebral folate deficiency; that bovine milk can promote folate receptor blocking antibodies; and that petitioners did not meet the required showing for an off-table case under the standard set out in *Althen*.[6]

1. The Special Master's Factual Finding that A.P.M Does Not Have Any Form of a Cerebral Folate Deficiency

Petitioners first object to the Special Master's decision to reject both the theory of their expert, Dr. Shafrir, and the diagnosis of the treating physician, Dr. Frye, that A.P.M. suffered from some type of cerebral folate deficiency. Mot. at 19–24. They contend that in making this determination, the Special Master failed to apply the correct analytical standard set forth in *Althen*. Mot. at 21. Petitioners note that *Althen* provides that "'sequence[s] hitherto unproven in medicine' may be supported by indirect evidence to resolve 'close calls regarding causation . . . in favor of injured claimants,'" and argue that, to the contrary, the Special Master required "conclusive medical literature" to support causation. Mot. at 21 (quoting *Althen*,

[6] The second and sixth objections appear to be overlapping or duplicative, *see* Mot. at 23–24, 29–30, and for that reason are considered together.

418 F.3d at 1280). Petitioners argue that whether A.P.M. suffered from cerebral folate deficiency or some milder syndrome does not matter, so long as they provide evidence that the "the existence of high levels of folate receptor antibodies coupled with low MTH[F] levels, albeit in the low normal range," can explain A.P.M.'s symptoms. *Id.*

The causation theory of petitioners is that a DTaP vaccination caused the production of autoantibodies that blocked the folate receptor, resulting in some form of cerebral folate deficiency. *See* Mot. at 4. Because the existence of this deficiency was a critical link in the posited chain of causation, and was disputed by the Secretary, it was entirely appropriate for the Special Master to determine at the outset whether the record evidence supported it. *See Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). While the Special Master did acknowledge that there is "scientific support for the effect that blocking autoantibodies can have on the process of delivering folic acid to the brain," Decision at 32, the Special Master rejected both of the petitioners' diagnoses because they each "failed to explain why a low normal reading [of folate in the CSF] could still be significant." *Id.* at 33.

In making this determination, the Special Master did not raise the burden of proof above what *Althen* dictates, but instead based his findings on a thorough and careful weighing and assessment of the record evidence, including the expert witness testimony. *See* Decision at 31–36. The expert witnesses on both sides agreed that a diagnosis of cerebral folate deficiency was incorrect, as A.P.M. did not exhibit any of the severe clinical symptoms of that disorder. Tr. at 114, 189, 204, 249, 288; *see also* Ramaekers I at 1985 (describing the "major manifestations" of cerebral folate deficiency). Even the treating physician, Dr. Frye, acknowledged that A.P.M. did not suffer from the "very striking neurological features" of this "severe disorder." Pet'rs' Ex. 16 at 35.

Moreover, these severe symptoms are linked to an abnormally low level of folate making its way to the brain --- hence, the term "deficiency." *See* Tr. at 348, 429; Ramaekers I at 1985–86. But the test of A.P.M.'s folate level in his CSF showed it to be in the normal range. Pet'rs' Ex. 16 at 22. [7] Although petitioners' expert testified that he believed the measurement was too high due to the presence of blood in the cerebrospinal fluid, Tr. at 133–34, 203–04, 449–51, the Special Master was persuaded by the contrary testimony regarding laboratory procedures offered by respondent's expert, *see* Decision at 33 (citing Tr. at 439) --- which is entirely appropriate, *see Moberly*, 592 F.3d at 1325–26. He also explained how the records of the test supported the determination that the level measured was reliable. Decision at 33 (discussing Pet'rs' Ex. 16 at 10–11). In rejecting Dr. Frye's diagnosis of cerebral folate deficiency, the Special Master "considered the relevant

[7] Petitioners admit that A.P.M.'s folate level was in the range considered to be "low *normal*." Mot. at 22 (emphasis added).

evidence in the record as a whole, [drew] plausible inferences from that evidence, and articulated a basis for his decision which is rational." *Hines ex rel. Sevier*, 940 F. 2d at 1527.

Turning to the alternative diagnosis of some sort of milder syndrome based on a high level of folate receptor blocking antibodies --- which petitioners' expert conceded "hasn't been delineated yet," Tr. at 161 --- the Court cannot find that the Special Master was arbitrary in his determination that petitioners failed to prove the existence of such a syndrome. The Special Master considered the reliability of the testimony of the expert witnesses and reasonably found that the petitioners' expert, Dr. Shafrir, lacked the expertise to explain the significance of a low but normal level of folate in the CSF, or of a high level of folate receptor antibodies. *See* Decision at 33–34; *see also id.* at 38; Tr. at 228 (Dr. Shafrir conceding his limited experience with cerebral folate deficiency). The Special Master also rationally explained why he did not find that the medical literature relied upon by petitioners was persuasive and probative. Decision at 33–35. He correctly noted, for instance, that one article involved a study of children who suffered from the actual, severe symptoms of cerebral folate deficiency that are absent from A.P.M.'s clinical picture, *id.* at 34–35 (discussing Ramaekers I at 1986–87), and another study used a biased sample and discussed neither the cause nor the result of a high level of anti-folate receptor antibodies, *id.* at 35 (discussing R.E. Frye, et al., *Cerebral Folate Receptor Autoantibodies in Autism Spectrum Disorder*, 18 Molecular Psychiatry 369, 378 (2013) (Pet'rs' Ex. 50 Ref. 4)).

The Special Master also reasonably explained why he discounted the reports by petitioners that A.P.M. responded to folate supplementation. Decision at 35 (citing Tr. at 139–40, 295–97). And he articulated a rational basis for finding that a measurement of A.P.M.'s folate receptor autoantibody levels made four years after the DTaP vaccination was administered was not a reliable means of demonstrating the impact of that vaccination. *Id.* at 36. In sum, the Special Master neither applied the wrong standard nor was arbitrary in reaching his determination that A.P.M. did not suffer from a form of cerebral folate deficiency.[8]

2. Evidence that Cow's Milk Can Promote Blocking Antibodies

The second objection of petitioners is to the Special Master's discussion of the evidence in the record of the relationship between cow's milk and the production of the anti-folate receptor autoantibodies. Mot. at 23–24; *see also* Mot. at 29 (arguing that the Special Master relied on an insufficiently proven "factor unrelated"). Respondent's expert, relying on medical literature submitted by the petitioners, argued that on the basis of molecular mimicry,

[8] While the Special Master might have lacked a basis for concluding that A.P.M.'s "autoantibody test results were just outside the moderate range," Decision at 36, the Court finds this conclusion immaterial to the determination in question.

the presence of dairy food in A.P.M.'s diet would more likely explain any elevated levels of folate receptor blocking autoantibodies. *See* Tr. at 313–18 (discussing Vincent T. Ramaekers, et al., *A Milk-Free Diet Downregulates Folate Receptor Autoimmunity in Cerebral Folate Deficiency Syndrome*, 50 Developmental Medicine & Child Neurology 346–52 (2008) (Pet'rs' Ex. 50 Ref. 6) (Ramaekers III)).

The Special Master noted that the response of petitioners' expert consisted of "sweeping denials," to the effect that the contention would mean that A.P.M. should have suffered from the autoantibodies from birth and that all children would have the posited syndrome. Decision at 37 (citing Tr. at 110, 185–86). Petitioners now contend that the Special Master did not adequately account for Dr. Shafrir's argument, and for the timing of the onset of A.P.M.'s problems. Mot. at 23–24.

The Special Master's assessment of the reliability of petitioners' theory, however, was neither arbitrary nor improper. He did not find that cow's milk had been established as an alternative cause of A.P.M.'s high level of autoantibodies. Decision at 37. Rather, he found that petitioners' molecular mimicry theory of causation, based on the similarity between a protein in the pertussis portion of the DTaP vaccination and one in the folate receptor, could not adequately explain why a scientifically-recognized *greater* homology between cow's milk and the folate receptor could not also explain the elevated level of A.P.M.'s autoantibodies. *Id.* at 36–38. This is an appropriate manner of assessing a petitioner's case. *See Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012).

As the Special Master explained, medical literature introduced by the petitioners support a relationship between milk and the anti-folate receptor antibodies. One article discusses that there is a "91 percent similarity" between amino acid sequences in milk and in the folate receptors. Ramaekers I at 1991. Another article finds that "[i]n the [cerebral folate deficiency] syndrome, the clinical manifestations typically occur after the switch to bovine milk." Decision at 36 (quoting Ramaekers III at 346). This second article states that "[m]ilk contains substantial amounts of [folate receptor] and seems to present the triggering antigen for the autoantibody response," and later explains: "The antibody showed better reactivity with the [folate receptor] from bovine milk than with the [folate receptor] from human placenta, human milk, or goat milk, suggesting bovine [folate receptor] as the likely primary antigen." Ramaekers III at 350–51. Thus, petitioners' own submitted literature rebuts the arguments made by their expert concerning the impact of breast-feeding and the ability of cow's milk to generate these antibodies. The Special Master was correct in finding that "the homology between certain milk proteins and the folate receptor protein sequences is high --- far more so than what petitioners argued was sufficient

for the molecular mimicry process to work under their theory." Decision at 36–37 (citing Tr. at 185, 314–16).

In this discussion, the Special Master considered [T.M.]'s testimony that she had fed A.P.M. with cow's milk before the age of eighteen months, and that the removal of dairy products from A.P.M.'s diet improved his condition. Decision at 37 (citing Tr. at 47–48, 72–73, 109). And he also noted that the antibody levels at the time of A.P.M.'s test --- four years after the alleged onset of A.P.M.'s autism --- could plausibly relate to the consumption of cow's milk and dairy products in the intervening time period, based on the evidence in the record. *Id.* The Special Master's determination that petitioners' theory of a DTaP vaccination trigger did not adequately address the possibility that cow's milk could generate the autoantibodies in question was rationally articulated and supported by the record.

3. *Prong 1 of* Althen *--- Reliable and Persuasive Theory*

In order to establish the first prong of *Althen*, the "can cause" step, a petitioner "must show a medical theory causally connecting the vaccine and the injury." *Althen*, 418 F.3d at 1278. The Federal Circuit explained that the required theory could be demonstrated on the basis of expert testimony alone and did not need "confirmation of medical plausibility from the medical community or literature" or proof of "an injury recognized by the medical plausibility evidence and literature." *Id.* at 1279–81. The petitioners here object to the Special Master's rejection of Dr. Shafrir's theory of causation, arguing that the former employed a higher standard of proof than *Althen* allows. Mot. at 24–26. But the Special Master properly applied *Althen*, and this objection amounts to nothing more than a disagreement with his assessment of the evidence.

The Special Master rationally found that the petitioners fell short of offering preponderant evidence to support their claim. First, he explained that because of Dr. Shafrir's lack of "personal experience in studying or diagnosing cerebral folate deficiencies," he found "the evidentiary value" of petitioners' expert's opinions to be "greatly diminished." Decision at 38 (citing Tr. at 228). The Special Master then articulated reasonable grounds, supported by the record, for finding petitioners' theory to be "unreliable on several levels." *Id.* at 39. He explained that the medical and scientific literature that petitioners' expert relied upon as "demonstrating a link between the DTaP vaccine and the production of blocking antibodies" involved other vaccines and other illnesses, and that the literature cited for a purported link between autism and cerebral folate deficiency were simply not scientifically reliable. *Id.* at 39-40. And he reiterated the problems with a theory based on molecular mimicry which points to a more likely autoantibody generator than the DTaP vaccination. *Id.* at 40. Petitioners do not identify any errors in this analysis, but instead insist on the reliability and plausibility of their theory. Mot. at 24–26. But the burden was on them "to provide a reputable medical or scientific explanation

that pertains specifically to" their case, and the Special Master appropriately assessed the reliability of their expert's testimony. *Moberly*, 592 F.3d at 1322, 1325–26.

4. Prong 2 of Althen *--- Logical Sequence of Cause and Effect*

The second prong of the *Althen* framework requires a petitioner to demonstrate, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. Petitioners object to the Special Master's finding that the medical records do not support the contention that the DTaP vaccination caused A.P.M.'s autism and developmental problems. Mot. at 26–28. But while [T.M.] testified that A.P.M.'s speech and behavioral problems began to be noticed within three and one-half weeks of the administration of the July 14, 2006 vaccination, Tr. at 22–23, the Special Master correctly notes that the contemporaneous medical records do not reflect this. *See* Decision at 13, 42; Pet'rs' Ex. 1 at 8. Moreover, he accurately recounts how petitioners' recollections of the course and timing of A.P.M.'s speech and developmental problems varied when reported to different treaters. *See* Decision at 3–4, 42; *see also* Pet'rs' Ex. 1 at 7; Pet'rs' Ex. 7 at 9, 18–24; Pet'rs' Ex. 8 at 6, 11; Pet'rs' Ex. 12 at 6.

The Special Master articulated his basis for finding that the record was insufficient to show that A.P.M. "experienced a reaction to the vaccine sufficient to suggest he was undergoing an autoimmune process." Decision at 41. *Id.* Respondent notes that petitioners' own expert concluded that he could not more specifically identify the onset of A.P.M.'s symptoms than occurring before the age of eighteen months. Resp't's Br. at 18 (citing Tr. at 101–02, 198). The Special Master clearly considered all of the evidence in making his findings. Given the inconsistencies in the record, the Special Master's finding that the petitioners failed to establish by preponderant evidence a logical sequence of cause and effect is reasonable. *See Hines ex rel. Sevier*, 940 F. 2d at 1527.[9]

5. Prong 3 of Althen *--- Medically Acceptable Temporal Relationship*

The third prong of the *Althen* framework requires a petitioner to demonstrate, by a preponderance of the evidence, "a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278. This requirement demands "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's

[9] At the tail end of petitioners' sixth objection, they also argue that the Special Master "improperly favored an idiopathic explanation of the cause of A.P.M.'s 'autism.'" Mot. at 29. But the Special Master had not found that petitioners had carried their burden to establish a prima facie case, so this argument is inapt. *See Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1351–52 (Fed. Cir. 2010).

etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352 (*citing Pafford*, 451 F.3d at 1358). Thus, if symptoms manifest later or earlier than medically expected, it is less likely that the vaccine is the cause. *See id*.

Petitioners object to the Special Master's finding that they failed to establish a medically acceptable temporal relationship between the vaccination and the onset of A.P.M.'s illness. Mot. at 28–29. But the evidence they cite in support of their contention is an opinion piece which states, as the Special Master accurately quotes, "the latency period between vaccination and autoimmunity ranges from days to years." Decision at 43 (quoting Nancy Agmon-Levin, et al., *Vaccines and Autoimmunity*, 5 Nat.Rev. Rheumatol. 648, 648 (2009) (Pet'rs' Ex. 53, Ref. 10)). The Special Master correctly found that this is too broad to satisfy *Althen*. *See Pafford*, 451 F.3d at 1358. Nor is it sufficient to identify the time period found for other injuries caused by other vaccines. Although petitioners suggest that the Special Master was improperly requiring "a hard and fast deadline" for the onset of A.P.M.'s injury, Mot. at 28 (quoting *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1384 (Fed. Cir. 2015)), he was instead seeking some explanation of the temporal relationship. But petitioners' own expert could not provide one, other than the circular argument that it took as long as it did. *See, e.g.,* Tr. at 182–84; Decision at 43–44 (citing *Koehn v. Sec'y of Health & Human Servs.*, 773 F.3d 1239, 1244 (Fed. Cir. 2014)). The Special Master did not arbitrarily determine that petitioners failed to satisfy this prong of *Althen*.

III. CONCLUSION

For the foregoing reasons, petitioners' motion for review is **DENIED** and the decision of the Special Master is **SUSTAINED.** The Clerk of Court is directed to enter judgment for respondent.

IT IS SO ORDERED.

s/ Victor J. Wolski
VICTOR J. WOLSKI
Judge