In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 08-284V

(To be Published)

T.M. *and* R.R.M, *parents and natural guardians of* A.P.M., *a minor,*	*	Special Master Corcoran
Petitioners,	*	Filed: August 9, 2016
v.	*	Entitlement Decision; Diphtheria Tetanus and Acellular Pertussis and Haemophilus Influenza Type B ("DTaP-Hib") Vaccine; Autism Spectrum Disorder ("ASD"); Cerebral Folate Deficiency.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Robert Joel Krakow, Law Office of Robert J. Krakow, P.C., New York, NY, for Petitioners.

Lynn Elizabeth Ricciardella, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION[1]

On April 17, 2008, T.M. and R.R.M filed a petition on behalf of their child, A.P.M., seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program").[2] T.M. & R.R.M sought to establish that the Diptheria Tetanus acellular Pertussis ("DTaP") vaccine that A.P.M. received on July 14, 2006, precipitated some form of cerebral folate deficiency, which in turn caused an autistic regression manifesting as an Autism Spectrum

[1] Because this decision contains a reasoned explanation for my actions in this case, I will 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 (2012). As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole decision will be available to the public. *Id*.

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended, 42 U.S.C. §§ 300aa-10 through 34 (2012) ("Vaccine Act" or "the Act"). Individual section references hereafter will be to § 300aa of the Act.

Disorder ("ASD").

A hearing was held on July 28-29, 2015, and in the months following the parties submitted post-hearing briefs. Having completed my review of the evidentiary record and the parties' filings, I hereby **DENY** Petitioners' request for compensation, for the reasons stated below.

I. FACTUAL BACKGROUND

A. Pre-Vaccination History

A.P.M. was born on April 16, 2005, at the Avera McKennan Hospital in Sioux Falls, South Dakota following a mostly normal pregnancy complicated only by vaginal bleeding at fourteen weeks gestation and fetal bradycardia.[3] *See generally* Pet'rs' Ex. 2; *see also* Pet'rs' Ex. 4 at 11, 13, 18; Pet'rs' Ex. 7 at 19. A.P.M. had high bilirubin levels and was treated with a phototherapy blanket for a short time. Pet'rs' Ex. 1 at 15, 51.

Throughout the first eighteen months of his life, A.P.M. had several well-child visits. His pediatrician, Dr. Rick Kooima, consistently noted in the medical records that A.P.M. was 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. During this time, A.P.M. received the Hib, Pediarix, and Pneumonia vaccinations at his two-, four- and six-month visits. *Id*. According to T.M., A.P.M. was "ill and irritable" and showed obvious discomfort following the vaccinations received at his two- and four-month visits, but the records do not indicate any significant alarming reactions requiring additional treatment. Pet'rs' Ex. 63 at 3. Following his six-month vaccinations, however, T.M. called Dr. Kooima to report that A.P.M. had been "fussy" since receiving his immunizations. Pet'rs' Ex. 1 at 12.

Because of their concern about A.P.M.'s reactions to the vaccinations he previously received, T.M. & R.R.M asked their pediatrician to defer additional immunizations at the 12-month well-child visit in April 2006. Pet'rs' Ex. 1 at 11, 40. T.M. & R.R.M did not want A.P.M. to ever have the varicella vaccine, but informed A.P.M.'s treaters that they would consent to the Prevnar vaccination at the next well-child visit. *Id*. Prior to his July 2006 15-month well-child visit, T.M. & R.R.M brought A.P.M. back to see Dr. Kooima because of their concern that A.P.M. was breaking into a rash whenever his skin encountered a milk-based product. Pet'rs' Ex. 1 at 9, 48. Dr. 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 again noted to be "well-

[3] Bradycardia means slowness of the heartbeat, with the pulse rate slowing to less than 60. *Dorland's Illustrated Medical Dictionary* (32d ed. 2012) at 245 ("*Dorland's*").

developed." *Id.*

B. Vaccination and Subsequent Medical History

At his 15-month well-child visit on July 14, 2006, A.P.M. received the combination DTaP and Haemophilus influenza type B ("Hib") and measles, mumps, and rubella ("MMR") vaccines. Pet'rs' Ex. 1 at 1, 16, 38; Pet'rs' Ex. 63 at 3; Pet'rs' Ex. 34 at 10. In the interim period until A.P.M.'s next pediatric visit three months later (when he was 18 months old), almost no medical records shed light on his post-vaccination condition – and even fewer before his two-year visit, at which time the record first sets forth the most detailed initial questions about A.P.M.'s development. However, Petitioners have offered declarations intended to fill in those blank periods in the record.

Thus, twelve days after the vaccinations (or on July 26, 2006), T.M. avers that she called Dr. Kooima, alerting him that A.P.M. had a low-grade temperature and a rash. Pet'rs' Ex. 1 at 8. Then, according to her, "within weeks" of the July 14, 2006, vaccinations A.P.M. "began to lose some of the words he had been using." Pet'rs' Ex. 63 at ¶ 9. He also became socially withdrawn and stopped playing with his toys. *Id.* at ¶¶ 11-12. But with the exception of an additional phone call from T.M. reporting that A.P.M. was experiencing watery eyes and congestion, T.M. & R.R.M had no further contact with his pediatrician until A.P.M.'s 18-month well-child visit on October 18, 2006. Pet'rs' Ex. 1 at 8.

The contemporaneous medical records largely do not corroborate T.M.'s statements. The medical records from that 18-month well-child visit include notations of parental concerns about "talking," but also characterize A.P.M. as "very healthy" in growth and development. Pet'rs' Ex. 1 at 8, 37; Pet'rs' Ex. 21 at 32. T.M. testified, however, that in the ensuing months her concerns about A.P.M.'s speech loss intensified, as did A.P.M.'s gastrointestinal issues. Pet'rs' Ex. 63 at 4. But concerns about A.P.M.'s development were not thoroughly documented until his two-year well-child visit six months later, on April 17, 2007. Pet'rs' Ex. 1 at 7, 36. In response, Dr. Kooima referred T.M. & R.R.M to the "Birth to Three" Program and to Dr. Jerome Blake, a developmental pediatrician, at the Sanford Children's Specialty Clinic in Sioux Falls, South Dakota. *Id.*

Rebecca Morke, a certified nurse practitioner working with Dr. Blake, subsequently evaluated A.P.M. on May 10, 2007 (at which time A.P.M. was 25 months old), and diagnosed him as having "mixed developmental delays," having lost the approximately 6 to 10 words he had previously acquired and used between 18 and 20 months of age. Pet'rs' Ex. 13 at 17; *see also* Pet'rs' Ex. 8 at 6; Pet'rs' Ex. 7 at 24. A.P.M. was administered the Rockford Infant Developmental Evaluation Scales ("RIDES"), and the results were not encouraging: although now more than two years old, A.P.M. demonstrated expressive language in the 6-9 month range; receptive language

skills at the 9-12 month range; personal social/self-care skills in the 9-12 month range; gross motor skills in the 18-24 month range; and fine motor skills in the 12-15 month range. Pet'rs' Ex. 26 at 184-90. In response, Dr. Blake recommended a hearing evaluation, speech therapy, occupational therapy, and a genetics workup. *Id*.

A week later that same May, the Sioux Falls School District administered an education assessment, giving A.P.M. the Battelle Development Inventory. Pet'rs' Ex. 13 at 17-18. The results showed that A.P.M. was more than two standard deviations below average in the areas of person-social, adaptive, motor, cognitive, and communication. *Id*. Other tests demonstrated that he had difficulty with language and fine motor skills. *Id*. As a result, A.P.M. qualified for special education. *Id*.

In the ensuing months, A.P.M. began routinely going for sessions with a chiropractor and also began speech and occupational therapy. *See generally*, Pet'rs' Exs. 9, 28; *see also* Pet'rs' Ex. 35, part 1 at 33-34; Pet'rs' Ex. 8 at 6-8. T.M. provided such treaters with a variety of dates about the onset of A.P.M.'s symptoms. To some treaters seen in October, May, and June 2007, T.M. & R.R.M reported onset at anywhere from 18 to 24 months. Pet'rs' Ex. 7 at 9, 18; Pet'rs' Ex. 8 at 6. Frequently they identified the MMR vaccine (which, as discussed below, is no longer a component of Petitioners' case) as an aggravating factor. Pet'rs' Ex. 8 at 6. To others, T.M. identified 19 months as the time when A.P.M. began losing skills. *Id.* at 11. She also more broadly defined the period between 15 and 18 months as when she became concerned about his loss of skills. Pet'rs' Ex. 12 at 6. Notably, however, no treater associated A.P.M.'s developmental problems with his vaccinations, and thus all references to onset in this portion of the medical records contain only T.M. & R.R.M' recitation of when developmental problems began, rather than a physician's informed diagnosis.

C. A.P.M.'s Autism Diagnosis

On June 25, 2007, when providing a pediatric health history for A.P.M.'s chiropractor, T.M. noted that A.P.M. had "developmental disability – possibly autism." Pet'rs' Ex. 28, part 1 at 5-6. She reported therein that A.P.M. had a "tough time" with vaccinations and had lost speech within four to six weeks after the last round of vaccinations he had received in 2006. *Id*. She also reported breastfeeding A.P.M. until 18 months, at which point A.P.M. began to drink cow's milk. *Id*. The next month, A.P.M.'s chiropractor noted in a record that A.P.M. had normal development until his 15-month immunizations, at which point he developed autism. Pet'rs' Ex. 10 at 4, and Ex. 12 at 6.

However, on October 15, 2007, Sioux Falls School District administered an Autism Screening and found that A.P.M. did not meet the eligibility criteria for an ASD. Pet'rs' Ex. 13 at

18. A few days later on October 18, 2007, A.P.M. was again administered the RIDES, which showed some improvement particularly in the receptive language category. Pet'rs' Ex. 7 at 10-15. A.P.M. was thus diagnosed with mixed developmental delays. Pet'rs' Ex. 13 at 18.

Shortly thereafter, in November 2007, A.P.M. first went to Thoughtful House in Austin, Texas where he saw Dr. Byran Jepson, a DAN![4] doctor. Pet'rs' Ex. 11 at 7-11. The medical history contained in these documents (consistent with the prior medical record discussed above) notes that after A.P.M.'s "15 month [vaccinations] not a lot of reaction:" he was "just sore and fussy for a few days. Then 3 weeks later stopped speaking, completey [sic] gone in 3 to 4 mnths [sic]." *Id.* at 8. Upon visiting with Dr. Kooima later that month, Dr. Kooima again "reinforced the fact that [A.P.M.] should be seen by an autistic specialist as soon as possible." Pet'rs' Ex. 21 at 7.

On November 8, 2007, the T.M. & R.R.M returned to Sanford Children's Specialty Clinic, where Dr. Tracy J. Stephens, a psychologist, performed a psychological evaluation of A.P.M. Pet'rs' Ex. 13 at 19. At this time, A.P.M. was diagnosed with "autistic disorder" because he demonstrated many characteristics of an ASD, including expressive and receptive language delay. *Id.* Dr. Stephens drew this conclusion from A.P.M.'s score of 32.0 on the childhood autism rating scale ("CARS"), which indicated that he had "mild to moderate" autism. Pet'rs' Ex. 7 at 27-29.

That 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 DSM-IV criteria. Pet'rs' Ex. 12 at 6-9. She noted that A.P.M. had lost skills after his 15-month vaccinations and currently had skill deficits in the areas of cognitive development, communication, socialization, and adaptive behavior. *Id.* Notably, she independently performed a CARS evaluation and rated A.P.M. at 23.0, a significantly lower score than what is required for an autism diagnosis.

[4] DAN! was composed of doctors and medical professionals who believed, among other things, that autism could be caused by vaccines. *See Dwyer v. Sec'y of Health & Human Servs.*, No. 03-1202V, 2010 WL 892250, at *165 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). The Autism Research Institute ("ARI"), which was founded by Bernard Rimland, MD in 1967, created the DAN! Protocol in 1995. *Moving Forward: The Expanding Mission of ARI*, Autism Research Institute, http://www.autism.com/expanding_2014 (last visited Aug. 9, 2016). "DAN! Doctors [were] trained in an approach to autism treatment that begins with the idea that autism is a biomedical disorder caused by a combination of lowered immune response, external toxins from vaccines and other sources, and problems caused by certain foods." DAN! PROTOCOL, Autism Services and Resources Connecticut, http://www.autismconnecticut.org/dan-protocol (last visited Aug. 5, 2016). Accordingly, DAN! "doctors may recommend treatments including nutritional supplements, special diets, testing for hidden food allergies, treatment of intestinal yeast or bacterial overgrowth, and detoxification of heavy metals." *Id.*

However, ARI discontinued the DAN! Protocol in 2011, noting that individuals included on the list of providers were merely doctors who attended training seminars, and there was therefore no way to assure that such practitioners were providing high quality services. Lisa Jo Rudy, *What Was the DAN! (Defeat Autism Now) Protocol?*, Very Well (updated Dec. 30, 2015), https://www.verywell.com/dan-defeat-autism-now-is-no-more-3971489 (last visited Aug. 5, 2016).

Id. However, she still recommended developmental therapy at a minimum of 25 hours per week. *Id*.

The Sioux Falls School District altered their determination about A.P.M. a week later, after administering the Bayley Scales of Infant Development, which put him at a developmental age of 19 months, even though he was 31 months old. Pet'rs' Ex. 14 at 20-24. The School District also administered the Gilliam Autism Rating Scale, which put A.P.M. in the average to high probability range for autism. *Id*. Ultimately, they concluded that he was eligible for special education as a result of his autism. *Id*. at 1-16.

D. Efforts to Treat A.P.M. and Identify the Cause of his ASD

Over the next several years, T.M. & R.R.M continued to pursue treatment for A.P.M. On November 19, 2007, T.M. & R.R.M took A.P.M. back to Thoughtful House, where he was seen by Kelly Barnhill, a nutritionist. Pet'rs' Ex. 11 at 2-7. At this time, T.M. & R.R.M informed Ms. Barnhill that at 18 months, A.P.M. had begun drinking cow's milk and seasonal allergies followed shortly thereafter. *Id*. Ms. Barnhill recommended many nutritional supplements. *Id.* A.P.M. was also seen at that time by Lucas Ramirez, a nurse practitioner, who diagnosed A.P.M. with unspecified metabolism disorder, immune mechanism disorder, nutritional deficiency, and encephalopathy after T.M. & R.R.M reported that he had experienced developmental regression a month after receipt of the MMR vaccine (or at approximately 16 months). Pet'rs' Ex. 18, part 1 at 37-42. Again, however – the medical records at this point temporally contain no treater opinion agreeing with T.M. & R.R.M that A.P.M.'s developmental problems related to any vaccination he had received.

Four months later, in February 2008 (at which time A.P.M. was nearly three years old), T.M. & R.R.M brought A.P.M. to see Dr. Michael Reiff, a developmental pediatrician, and Dr. Robin Rumsey, a pediatric neurologist, at the Autism Spectrum Disorders Clinic at the University of Utah. Pet'rs' Ex. 1 at 55-72. Based on several tests administered, A.P.M. (who was now nearly three years old) was determined to have the overall development level equivalent to a 19 to 20 month-old child. *Id*. These treaters recommended that T.M. & R.R.M have A.P.M. undergo genetic testing, particularly fragile x testing, and referred Petitioners to Dr. Khalid Khan, a pediatric gastroenterologist, at the University of Minnesota. *Id*. But such testing found "no numerical or structural chromosomal abnormality" and also did not find the "fragile x chromosome." Pet'rs' Ex. 13 at 1-16.[5]

[5] At most, genetic testing performed at the University of Minnesota identified a copy number loss within 14q32.33 (Pet'rs' Ex. 15) – but T.M. shares that same loss without any similar or identifiable symptoms. Pet'rs' Ex. 18, part 1 at 28-29.

It was not until 2010, however – almost four years after the July 2006 vaccinations – that any treater formally suggested that A.P.M.'s developmental problems were vaccine-related.[6] On February 17, 2010, A.P.M. first saw Dr. Richard Frye, a child neurologist, at the University of Texas. Pet'rs' Ex. 16 at 52. In his contemporaneous notes from the visit, Dr. Frye stated that A.P.M. had "high functioning autism [with] an abnormal EEG[7] and staring episodes," and recommended further EEG studies and additional testing. In particular (and as discussed in more detail below), Dr. Frye was interested in evaluating whether A.P.M.'s autism might be linked to the amount of folate his brain was receiving.

At Dr. Frye's direction, A.P.M. underwent testing for the presence of folate receptor blocking and binding autoantibodies in October 2010 at the State University of New York Downstate Medical Center in Brooklyn, New York. Pet'rs' Ex. 16 at 38-39. The testing results (notably, performed four years after the relevant vaccinations) revealed that A.P.M. had a folate transporter blocking autoantibody titer of 1.19 pmoles/ml. *Id.* at 38. Based upon a range dependent on levels found for "normal population, women with neural tube defect and children with [cerebral folate deficiency] syndrome," the measured amount fell on the "high" end of the range, because the titer exceeded 1.0 pmoles/ml (with a "medium" range specified as .6 – 1.0). *Id.* Notably, however, a patient summary chart prepared for A.P.M. by Dr. Frye's office in 2014 characterized the same titer value (based on the same October 2010 testing) as merely falling in the "medium" range (consistent with the medium range if the 1.19 value was rounded down). Pet'rs' Ex. 64 at 40.

Dr. Frye reviewed the results with Petitioners in December 2010. He expressed the opinion that the blocking autoantibodies were in the high range, and therefore possibly indicative of a shortage (deficiency) of the B-vitamin folate (also called vitamin B9) in the brain – amounting to a cerebral folate deficiency.[8] Pet'rs' Ex. 16 at 35-36. However, Dr. Frye misstated in his written

[6] During this time, A.P.M. continued being seen by Thoughtful House (now known as the Johnson Center) on a regular basis. *See generally*, Pet'rs' Ex. 18, part 1. On August 2, 2010, Dr. Jepson wrote a letter exempting A.P.M. from any future immunizations. Pet'rs' Ex. 39 at 5; Pet'rs' Ex. 34 at 9; Pet'rs' Ex. 18, part 1 at 13.

[7] An EEG is an electroencephalogram. *Dorland's* at 594.

[8] Cerebral folate deficiency is a neurological syndrome associated with low levels of 5-methyltetrahydrofolate ("MTHF"), the active folate metabolite, as measured in cerebral spinal fluid samples and in contrast to normal levels in blood serum. Tr. at 117-20 (citing Pet'rs' Ex. 50, Ref 1 (Vincent T. Ramaekers, et al., Autoantibodies to Folate Receptors in the Cerebral Folate Deficiency Syndrome, 352(19) N. Engl. J. Med 1985 (May 12, 2005) ("Ramaekers I")). The MTHF transported across the blood-brain and blood-cerebral spinal fluid barriers is mediated primarily by membrane-associated folate receptors. Ramaekers I at 1985. It has been hypothesized that impairments in folate transport across the blood-cerebral spinal fluid barrier is caused by circulating autoantibodies that prevent folate from binding to certain folate receptors. *Id.* at 1986. Insufficient levels of folate within the central nervous system have been linked to neuropsychiatric disorders, with the first clinical manifestations of cerebral folate deficiency reported as having appeared after the age of four to six months. *Id.* at 1990-91.

record the titer value as 1.9, rather than the actual result of 1.19 (an amount significantly lower). *Id.* at 35. He also acknowledged that A.P.M.'s presentation did not precisely fit the usual clinical indicia of cerebral folate deficiency. Thus, he noted that children with a definitive cerebral folate deficiency diagnosis (who would similarly have high levels of the blocking autoantibodies) presented with striking, degenerative neurological features that A.P.M. had not experienced. *Id.* ("children with the severe disorder usually are blind very early in life").

In light of the findings, Dr. Frye concluded that "it is very possible that [A.P.M.] has a mild form" of a cerebral folate deficiency. Pet'rs' Ex. 16 at 35. To confirm the proposition, Dr. Frye scheduled a lumbar puncture in order to measure A.P.M.'s folate level in his cerebral spinal fluid ("CSF")[9] (a more direct indication of the presence of a cerebral folate deficiency). Pet'rs' Ex. 16 at 35.

A spine lumbar puncture and a brain MRI were thereafter performed on A.P.M. on March 30, 2011. Pet'rs' Ex. 64 at 40; Pet'rs' Ex. 16 at 10, 47-50. The MRI results were deemed normal. *Id.* at 47-50. Details of the lumbar puncture procedure, however, require explication, given the extent to which (as discussed below) the parties dispute the procedure's adequacy. The notes from the date of testing state as follows:

> An interspinous lumbar puncture was carried out under fluoroscopic guidance with a 25 gauge short spinal needle at the level of L3-4 under sterile conditions. A total amount of 10 cc of CSF was withdrawn. *CSF was initially slightly blood-tinged but cleared.*
>
> 3.5 cc of CSF was distributed in appropriate amounts into the required *containers* and delivered to the neurology lab. The remaining 6.5 cc of CSF were submitted to the general lab for routine analysis. Opening pressure measured 24 cm water. *No complication was noted.*
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> ***
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> *Impression: Technically successful fluoroscopically guided lumbar puncture.*

[9] Cerebrospinal fluid ("CSF") is a "clear, colourless liquid that fills and surrounds the brain and the spinal cord and provides a mechanical barrier against shock" and "transports metabolic waste products, antibodies, chemicals, and pathological products of disease away from the brain and spinal-tissue into the blood stream." *Encyclopedia Britannica Online*, Encyclopedia Britannica Inc. (2016), *available at* https://www.britannica.com/science/cerebrospinal-fluid (last accessed Aug. 5, 2016). Examination of the CSF through a lumbar puncture (or spinal tap) can be used to diagnose a number of diseases. *Id.*

Id. at 10-11 (emphasis added). Among other things, the lumbar puncture measured the amount of 5-methyltetrahydrofolate ("MTHF"), or active folate metabolite, in the CSF at the time as 53 nmols/L, an amount characterized as "within our reference range" of 40-128 nmols/L, and therefore normal. Pet'rs' Ex. 16 at 22. In a September 2011 note recording a discussion held with T.M. & R.R.M about the results of the CSF testing, Dr. Frye termed the folate levels measured as "low normal." *Id.* at 3.[10]

More tests were performed on A.P.M. to determine the extent to which he might be suffering from some kind of metabolic disorder. Thus, later in 2011, Dr. Frye conducted additional blood work that revealed an increased level of pyruvate in A.P.M.'s CSF. Pet'rs' Ex. 16 at 3. Dr. Frye noted, however, that he was "not sure what to make of the isolated increased CSF pyruvate as all of the other mitochondrial markers were negative." *Id.* In addition, organic acid testing conducted in May 6, 2012, was "not consistent with a known disorder of amino acid metabolism." Pet'rs' Ex. 27, part 2 at 18-28. A.P.M. also had hair and stool analyses in May 2012, both of which were normal. Pet'rs' Ex. 27, part 1 at 5-20.

On February 14, 2014, T.M. & R.R.M returned to see Dr. Frye, now at the Arkansas Children's Hospital, for formal consideration of whether A.P.M. had experienced a developmental encephalopathy, or could be diagnosed with a cerebral folate deficiency or some mitochondrial disorder that may have played a role in his developmental problems. Pet'rs' Ex. 46 at 1-3; Pet'rs' Ex. 64 at 39-40, 60-63. Dr. Frye at that time repeated the assertion that A.P.M. had a cerebral folate deficiency based on purported "below normal levels of folate in his cerebral spinal fluid," but did not elaborate on the existence of any measurements taken after the 2011 lumbar puncture (which, as noted above, showed folate amounts in the low normal range). Pet'rs' Ex. 46 at 1. A.P.M. was still seeing Dr. Frye on a regular basis as of May 2015. *See generally* Pet'rs' Ex. 64.

II. PROCEDURAL HISTORY

T.M. & R.R.M filed this action on April 17, 2008, as a short-form autism petition to be included in the Omnibus Autism Proceeding ("OAP").[11] Pet. (ECF No. 1). Thereafter, Respondent

[10] With the passage of time (and unbound by the aforementioned March 2011 CFS results – which from the record appears to be the sole instance A.P.M.'s CSF was tested) Dr. Frye greatly expanded his characterization of this reading. Thus, in a February 2014 note from a subsequent visit to his clinic by T.M. & R.R.M, Dr. Frye states that A.P.M. had been "diagnosed with cerebral folate deficiency with frank *below normal levels* of folate in his cerebral spinal fluid." Pet'rs' Ex. 46 at 1.

[11] This case was initially among the more than 5,400 cases initially filed under short form petition in the OAP, where thousands of petitioners' claims that certain vaccines caused autism were joined for purposes of efficient resolution. A "Petitioners' Steering Committee" was formed by many attorneys who represent Vaccine Program petitioners, with about 180 attorneys participating. This group chose "test" cases to represent the entire docket, with the understanding that the outcomes in these cases would be applied to cases with similar facts alleging similar theories.

filed her Rule 4(c) Report and identified certain deficiencies in the record. On June 22, 2008, Petitioners, in compliance with the initial order of the first special master assigned to the case (ECF No. 4), filed a Statement Regarding Onset. ECF No. 9. Respondent agreed that this case was timely filed and appropriate for inclusion in the OAP given A.P.M.'s ASD diagnosis. ECF No. 10.

After the conclusion of the OAP test cases in 2010, Petitioners opted to continue pursuit of their claim. To that end, T.M. & R.R.M 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 regression. ECF No. 24 at 4. A status conference was held on June 29, 2012, and the special master ordered Petitioners to file their medical records by July 30, 2012, and also to file a status report on or before August 13, 2012, advising the Court as to their efforts in locating an expert. ECF No. 27.

Petitioners complied and filed medical records on July 30, 2012 (ECF No. 28), but missed the deadline to update the Court on their attempts to obtain an expert. As a result, the special master issued an order to show cause as to why the case should not be dismissed by September 4, 2012. ECF No. 29. On the date of that deadline, Petitioners filed a response, explaining that their failure to comply was the result of a clerical error. ECF No. 30 at 3. But they also indicated that they were having difficulty obtaining expert support for their theory that a cerebral folate deficiency had caused A.P.M.'s developmental disorder and were considering alternative causal theories. *Id*. at 3, 5.

The Petitioners' Steering Committee chose six test cases to present two different theories regarding autism causation. The first theory alleged that the measles portion of the measles, mumps, rubella ("MMR") vaccine precipitated autism, or, in the alternative, that MMR plus thimerosal-containing vaccines caused autism, while the second theory alleged that the mercury contained in thimerosal-containing vaccines could affect an infant's brain, leading to autism.

The first theory was rejected in three test case decisions, all of which were subsequently affirmed. *See generally Cedillo v. Sec'y of Health & Human Servs.*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for review den'd*, 89 Fed. Cl. 158 (2009), *aff'd*, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec'y of Health & Human Servs.*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for review den'd*, 88 Fed. Cl. 473 (2009), *aff'd*, 605 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec'y of Health & Human Servs.*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for rev. den'd*, 88 Fed. Cl. 706 (2009).

The second theory was similarly rejected. *Dwyer v. Sec'y of Health & Human Servs.*, No. 03-1202V, 2010 WL 892250 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *Mead v. Sec'y of Health & Human Servs.*, No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010).

Ultimately a total of eleven lengthy decisions by special masters, the judges of the U.S. Court of Federal Claims, and the panels of the U.S. Court of Appeals for the Federal Circuit, unanimously rejected petitioners' claims. These decisions found no persuasive evidence that the MMR vaccine or thimerosal-containing vaccines caused autism. The OAP proceedings concluded in 2010.

In response, the special master ordered Petitioners to file an amended petition by September 13, 2012. ECF No. 31. Again, Petitioners requested an unopposed extension (ECF No. 32), which the special master granted. ECF No. 33. Petitioners filed their second amended petition on October 4, 2012, alleging that Petitioners would be proceeding on the basis of a challenge/rechallenge theory.[12] ECF No. 34. In the ensuing months, Petitioners struggled to complete the filing of medical records, requesting several extensions of time to do so but not completing the task until August 2013. ECF No. 60. By February 24, 2014 (one of several extended deadlines Petitioners were provided), T.M. & R.R.M requested an additional month to file their expert report or "take other appropriate action" as "[i]t is not clear at this juncture whether or not [P]etitioners will be able to produce an expert report supporting the Second Amended Petition." ECF No. 65 at 1. After several more extensions of time, however, Petitioners finally filed their expert report from Dr. Yuval Shafrir on August 25, 2014. ECF No. 74.[13]

In September 2014, the case was reassigned to me. ECF Nos. 76, 77. Following a status conference held on November 6, 2014, I ordered the Parties to submit a Joint Status Report proposing available hearing dates and extended Respondent's deadline for an expert report until January 30, 2015. ECF No. 78. A two-day entitlement hearing was set for July 28-29, 2015, in Washington, DC, and a pre-hearing schedule was set.

On January 28, 2015, Respondent requested a few extra days to submit her expert report, (ECF No. 81), and ultimately did file one from Dr. Max Wiznitzer, along with his curriculum vitae and a single medical article, on February 2, 2015. ECF No. 82. Petitioners and Respondent then filed their pre-hearing submissions on April 16, 2015, and May 15, 2015, respectively. ECF Nos. 83, 84. On June 11, 2015, Petitioners filed a supplemental expert report from Dr. Shafrir along with several additional pieces of medical literature. ECF Nos. 85-88.[14]

Petitioners and Respondent both filed their witness lists on June 15, 2015. ECF Nos. 94

[12] As noted in *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1322 (Fed. Cir. 2006), "[a] rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine."

[13] In the early spring of 2014, Petitioners expected to advance a theory that A.P.M. suffered from a mitochondrial disorder that, in conjunction with his vaccinations, caused his developmental regression. Mar. 26, 2014, Motion for Extension of Time (ECF No. 67) at 2-3. They offered two pieces of scientific literature in support of the theory. *See* Pet'rs' Exs. 46 and 48. However, the Petitioners subsequently backed away from this theory. May 27, 2014, Motion for Extension of Time (ECF No. 70) at 1 ("[t]he retained expert further advises counsel that his opinion is not predicated on a formal diagnosis of mitochondrial disease"). At hearing, mitochondrial disease was not discussed (except in passing), and Petitioners' theory does not propose that A.P.M. had such a metabolic disorder.

[14] Dr. Shafrir's updated curriculum vitae, along with annotations of the formerly filed exhibits and a corrected version of a typographical error in his supplemental report, were all filed on June 15, 2015. ECF Nos. 89-93.

and 96. Petitioners also filed several more exhibits – as well as a third amended petition, which entirely disposed of the challenge/rechallenge theory set forth in their second amended petition, asserting instead that the vaccines administered to A.P.M. caused a cerebral folate deficiency, which in turn precipitated developmental regression, developmental delay, apraxia of speech, and multiple physiological symptoms. ECF No. 97. They also filed more medical records and their response to Respondent's pre-hearing memorandum (ECF Nos. 98-101), and then even more medical literature. ECF Nos. 103 and 105.

The entitlement hearing took place as scheduled on July 28-29, 2015, and I thereafter set the schedule for the parties' post-trial briefings. On August 19, 2015, Respondent filed additional medical literature she had identified at the entitlement hearing. ECF No. 107. After two extensions of time, Petitioners filed their post-hearing brief along with even more medical literature on November 10 and 11, 2015. ECF Nos. 114 and 115 ("Post-Trial Brief"). Respondent asked for similar extensions, filing her post-hearing brief on January 11, 2016. ECF No. 124.[15] Petitioners followed with an additional supplemental report by Dr. Shafrir on the protein homology issue on February 3, 2016 (ECF No. 128), and then filed their response to Respondent's post-hearing memorandum on February 10, 2016. ECF No. 129 ("Reply").

III. TESTIMONY PRESENTED AT HEARING[16]

A. T.M.

T.M., A.P.M.'s mother, was the only fact witness testifying at the hearing. *See generally* Tr. at 4-87. She provided a narrative about A.P.M.'s development, with particular emphasis on the differences she observed in his behavior after the 15-month vaccinations.

T.M. testified that she witnessed A.P.M. experience varied reactions to the vaccines he had received. Thus, after receiving some initial childhood vaccinations on June 14, 2005, and August 16, 2005, respectively, A.P.M. was "ill and irritable" and "showed signs and symptoms of severe pain and discomfort." Pet'rs' Ex. 63 at 2. He had a fever and was screaming, and was thereafter inconsolable for weeks despite T.M.'s efforts to comfort him. *Id.*; Tr. at 11-13. His reaction to his six-month vaccinations, however, was less notable, characterized only by a fever

[15] On December 21, 2015, a stipulation for an award of interim attorney's fees was filed (ECF No. 117), and that same day I issued a decision granting an award of fees based on the stipulated sums. ECF No. 120. Judgment for the interim award entered on December 23, 2015. ECF No. 122.

[16] Besides the records previously discussed, the witness testimony, and medical and scientific literature offered in this case, Petitioners also filed a lengthy compilation of photographs intended to display A.P.M.'s condition at various points in his life, and thereby illustrate their arguments about the course of his regression. *See generally* Pet'rs' Ex. 65 (ECF No. 100). The photos were not discussed at hearing, however, and (having reviewed them), I do not find that they aid Petitioners in meeting their evidentiary burden in this action.

and rash. Tr. at 14. A.P.M. otherwise continued to meet his developmental milestones during this time period. *Id*. He was using approximations of 20 to 30 words, "although many of his words were garbled and difficult to understand." Pet'rs' Ex. 67 at 2; Tr. at 18, 33. He also played well with other children and was "happy." Pet'rs' Ex. 67 at 2. T.M. testified that he was "nothing different than my daughter." Tr. at 7.

A.P.M.'s reactions to the DTaP and MMR vaccines administered in July 2006, however, were in her view qualitatively different. Within three or four weeks following his receipt of the MMR and DTaP-Hib vaccines on July 14, 2006, she testified, A.P.M. became "socially withdrawn and fearful." Pet'rs' Ex. 67 at 2; Tr. at 19-20. He lost interest in toys, stopped using many of the words he had used previously, and was less interactive. *Id*. at 3; Tr. at 22-23. T.M. characterized the change as "[n]ight and day, completely," although she also expressed the view that the regression was also "gradual" in nature. Tr. at 25, 32. A.P.M. also began engaging in repetitive routines in September 2006, such as pressing his face against the liquid-crystal-display ("LCD") television. *Id*. at 24-25. A.P.M.'s gastrointestinal issues intensified greatly during this period. Pet'rs' Ex. 67 at 3. Overall, it seemed to T.M. as if A.P.M. "kind of started to disappear." Tr. at 28.

T.M. conceded that the record does not document her concerns about A.P.M.'s developmental problems before his 18-month visit with Dr. Kooima in October 2006 – three months after the vaccinations in question – and that this record actually stated that (as of that time) A.P.M. was healthy and developing normally. Tr. at 34-35, 71, 74. She attributed this in part to the fact that she and her husband had disagreed whether A.P.M.'s developmental problems were significant enough to warrant professional attention. *Id.* at 27-28. She also asserted that she had attempted to call Dr. Kooima's office concerning A.P.M.'s initial reactions to his 15-month vaccines "multiple times." *Id*. at 71-72. Only at A.P.M.'s two-year well-child visit, however, did the records reflect T.M.'s report to a treater about her concern that A.P.M. had an ASD, leading Dr. Kooima to concur and provide T.M. & R.R.M with developmental assessment specialist referrals. *Id*. at 35-36.

T.M. was asked some questions about A.P.M.'s alleged cerebral folate deficiency and efforts to treat it. She noted that for several years, and at Dr. Frye's recommendation, A.P.M. had been receiving some form of leucovorin,[17] which contains "super-high doses of folinic acid" and therefore could help alleviate his purported folate deficiency. Tr. at 48-50, 60-62. Dr. Frye recommended this course of action in reaction to A.P.M.'s high levels of folate receptor blocking autoantibodies as measured in 2010 by the SUNY Downstate Center. *Id*. at 52-54. She also

[17] Leucovorin is in a class of medications called folic acid analogs. *Dorland's* at 1026. It is a metabolically active form of folic acid that has been used in cancer therapy to protect normal cells against methotrexate – called also *citrovorum factor, folinic acid. Id.*

admitted that up to the date of the 18-month well-child visit, she had "exclusively" nursed A.P.M., but around that time started him on cow's milk. Tr. at 72-73. Not long after bovine milk was introduced into A.P.M.'s diet, however, he broke out in eczema. *Id*. at 73. She therefore hypothesized that A.P.M. had a lactose intolerance. *Id*. at 83-84. As a result, in July 2007, and with the added urging of certain treaters, T.M. & R.R.M put A.P.M. on a dairy-free diet, which in her opinion had lessened his aggression. *Id*. at 47-48; 83.

Currently, T.M. stated, A.P.M. is "doing phenomenal" and is a "very, very high-functioning" child despite continuing to have developmental issues. Tr. at 46, 59. Even though he does not engage in back-and-forth dialogue much, he now has some conversational language. *Id*. Indeed, his improvement is such that some people do not even realize A.P.M. has been diagnosed with autism. *Id*. at 59.

B. Petitioners' Expert – Dr. Shafrir

Dr. Yuval Shafrir is a child neurologist who graduated from the Sackler School of Medicine at Tel Aviv University in 1982. Tr. at 88; Pet'rs' Ex. 62 at 1. He thereafter did residencies in pediatrics at Kaplan University and the Bellinson Medical Center in Israel. Pet'rs' Ex. 62 at 1. Dr. Shafrir went on to do residencies in pediatrics at North Shore University Hospital in New York, and in pediatric neurology at the Washington University Medical Center in Missouri. *Id*. at 1-2; Tr. at 88. From 1992 to 2000, Dr. Shafrir worked at a number of different U.S. hospitals. Tr. at 88. Currently, he practices pediatric neurology in private practice affiliated with Sinai Hospital in Baltimore. *Id*. at 91. He is licensed to practice medicine in Maryland, and has board certifications in child neurology, although he has not renewed his board certification in pediatrics. *Id*. at 88. He has worked and taught across the country in pediatrics and neurology and presently does so 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.

Dr. Shafrir described himself as an "epileptologist by training" and general pediatric neurologist. Tr. at 91. He testified as an expert in pediatric neurology. *Id.* at 94. He claims to have experience treating individuals suffering from immune system-mediated conditions as well. *Id.* He is not, however, an expert in immunology, metabolic conditions, or the specific topic of cerebral folate deficiency. *Id.* at 228 (admitting that this was the first case in which Dr. Shafrir had even considered the subject, although he "read about the syndrome and . . . knew about it"). He is also not one of A.P.M.'s treating physicians and has never examined A.P.M. himself. *Id*. at 94-95. Over the course of his career, he has seen approximately 1,500 ASD patients. *Id*. at 91, 104. But he does not have an academic background in studying or researching ASDs. *See generally* Pet'rs' Ex. 62.

Dr. Shafrir primarily opined that A.P.M. developed autistic regression as a result of what he termed "an autoimmune anti-folate receptor antibody syndrome," precipitated by receipt of the

DTaP vaccine. Tr. at 95. He distinguished this from cerebral folate deficiency, acknowledging that A.P.M.'s presentation was not consistent with "the current clinical picture of cerebral folate deficiency." *Id.* at 201. Dr. Shafrir thus disputed Dr. Frye's assertions (as set forth in the medical record) that a cerebral folate deficiency diagnosis was appropriate, since the levels of folate measured in A.P.M.'s CSF were not below normal (although Petitioners nevertheless assert that the "low normal" measurements had clinical significance). *Id.* at 204-07.

The core of Dr. Shafrir's opinion arose from the results of the October 2010 testing performed on A.P.M. that revealed high levels of the folate receptor blocking autoantibodies. Tr. at 113. Even though the testing results alone are not equivalent to a formal diagnosis that A.P.M. had a true cerebral folate deficiency, high blocking autoantibody levels had been shown to have significance to the condition. *See generally* Pet'rs' Ex. 50, Ref 1 (Vincent T. Ramaekers, et al., Autoantibodies to Folate Receptors in the Cerebral Folate Deficiency Syndrome, 352(19) N. Engl. J. Med 1985 (May 12, 2005) ("Ramaekers I")).

As Dr. Shafrir testified, the authors of Ramaekers I examined serum specimens taken from 28 children already diagnosed with a cerebral folate deficiency (due to the presence of severe neurologic symptoms akin to those already mentioned, such as "marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal tract sings in the legs, dyskinesias . . . , and in some cases, seizures"). Tr. at 118-27, Ramaekers I at 1985. That study determined that the subjects also had high levels of the folate receptor blocking autoantibodies – suggesting that the cerebral folate deficiency was the "consequence" of impairment of the folate transport process caused by the presence of the blocking autoantibodies. Ramaekers I at 1990. Ramaekers I did not, however, propose how the blocking autoantibodies *themselves* came to be, other than to speculate that (a) they were produced in the first four to six months of a child's life, and (b) they might have been "induced by soluble folate-binding proteins in human or bovine milk *or* result from sensitization by *unknown* antigens with similar epitopes."[18] *Id.* at 1991 (emphasis added).

Dr. Shafrir opined that the "unknown antigens" were derived from the pertussis component of the DTaP vaccine. Tr. at 163-64.[19] The antibodies subsequently produced attacked A.P.M.'s folate receptor molecule. Tr. at 113, 176. The blocking, Dr. Shafrir asserted, led to a milder,

[18] An epitope is also known as an antigenic determinant – which is part of an antigen that is recognized by the immune system and capable of stimulating an immune response. *Dorland's* at 502, 637.

[19] At trial, Petitioners abandoned a prior element of their claim: that the MMR vaccine played a role in A.P.M.'s regression. Tr. at 443, 457; Post-Trial Brief at 19 n.5. They did so because, as Dr. Shafrir admitted, he could not identify any homology between the peptide sequences of any MMR vaccine components and the sequences comprising the folate receptors to which the vaccine antigens would be presented and initiate the autoimmune production of self-attacking antibodies. Tr. at 443-44, 474.

cerebral folate deficiency-like syndrome for A.P.M. that may not have had the hallmarks of the more severe form of the disease, but nevertheless manifested as autism. *Id*. at 183-84.

To explain how the DTaP vaccine actually caused the production of the blocking autoantibodies, Dr. Shafrir proposed the mechanism of molecular mimicry. He thus discussed the concept of homology – "identical sequences of amino acids of two different proteins." Tr. at 142, 157, 161-65, 173, 220-25 (citing Pet'rs' Ex. 53, Ref. 6; Pet'rs' Ex. 53, Ref. 7 (G. Lucchese, et al., *Peptidology: Short Amino Acid Modules in Cell Biology and Immunology*, 33 Amino Acids 703 (2007) ("Lucchese I"))); Pet'rs' Ex. 53, Ref. 8 (G. Lucchese, et al., *The Peptide Network between Tetanus Toxin and Human Proteins Associated with Epilepsy*, 2014 Epilepsy Research and Treatment, *available at* http://dx.doi.org/10.1155/2014/236309 ("Lucchese II"))).[20] Peptide similarity can cause the production of antibodies that attack the self due to the body's inability to distinguish the between self and a foreign antigen. *Id*. at 159, 170 (citing Pet'rs' Ex. 53, Ref. 5 (G. Poland, et al., *Vaccinomics, Adversomics, and the Immune Response Network Theory: Individualized Vaccinology in the 21st Century*, 25(2) Semin. Immunol. 89 (Apr. 2013))). Dr. Shafrir proposed that a five-peptide sequence in the pertussis component of the DTaP vaccine had sufficient homology with proteins in the cerebral folate receptors to initiate an autoimmune process, attempting to demonstrate the claimed homology based upon a number of articles discussing protein chain sequences. Tr. at 165.

Dr. Shafrir admitted that (unlike with milk) there is no proven or studied homology between the folate receptor and the components of *any* vaccines – nor could he establish the larger concept that a vaccine could cause the production of the blocking autoantibodies by any mechanism. Pet'rs' Ex. 50 at 31-32. He therefore relied on instances in which other vaccines have been deemed causally related to autoimmune disorders. Tr. at 155-56 (citing Pet'rs' Ex. 53, Ref. 10 (Nancy Agmon-Levin, *Vaccines and Autoimmunity*, 5 Nat. Rev. Rheumatol. 648 (2009) ("Agmon-Levin"))). Agmon-Levin, a review article, broadly considers the propensity of different vaccines to produce autoimmune illnesses, and in the course of its overview discusses a variety of mechanisms by which the illness can occur, such as molecular mimicry. Tr. at 157-58; Agmon-Levin at 650, Box 2. Because, Dr. Shafrir opined, the anti-folic acid receptor antibody syndrome that A.P.M. had was autoimmune in origin, it too could be vaccine-caused. Tr. at 161.

[20] A significant amount of time at hearing was devoted by both experts to contesting the issue of homology. Petitioners offered numerous exhibits to support their claim that homology exists. *See, e.g.*, Pet'rs' Ex. 53, Ref. 6; Lucchese I; Lucchese II; Pet'rs' Ex. 53, Ref. 9; Pet'rs' Ex. 73 (Rodrigo Villarino Romero, et al., *Filamentous Hemagglutinin of Bordetella Pertussis: a Key Adhesin with Immunomodulatory Properties*? 9(12) FUTURE MICROBIOL. 1339 (2014)). Indeed, Petitioners even submitted an additional expert report from Dr. Shafrir post-hearing, attempting to refute Dr. Wiznitzer's claim that there was insufficient homology between pertussis components and the folate receptors. Pet'rs' Ex. 74. This is despite the fact that *neither* expert is an immunologist, and therefore neither has the professional expertise to opine on such issues (beyond their general medical training and personal familiarity with molecular biology).

Next, Dr. Shafrir discussed the scientific support linking the presence of cerebral folate receptor blocking autoantibodies with developmental regression or autism. The mere fact that A.P.M. possessed a high level of the blocking autoantibodies, and the fact that he was also diagnosed as autistic, was in his view important, given that a significant portion of the children studied in Ramaekers I also were autistic (although they also unquestionably suffered from cerebral folate deficiency based on symptomatology not possessed by A.P.M.). Tr. at 119 (citing Ramaekers I at 1989). But Dr. Shafrir also stressed the strong correlation between cerebral folate deficiency and autistic syndrome that he claimed was documented in several relevant studies. Tr. at 201-02, 218-19. For example, in a second Ramaekers article also offered in support of the purported autism-cerebral folate deficiency link (Pet'rs' Ex. 50, Ref. 3 (V.T. Ramaekers, et al., *Folate Receptor Autoimmunity and Cerebral Folate Deficiency in Low-Functioning Autism with Neurological Deficits*, 38 Neuropediatrics 276 (2007) ("Ramaekers II"))), 25 children suffering from infantile-onset cerebral folate deficiency (and thus in possession of the same kind of severe symptoms not characterizing A.P.M.'s condition) were studied, with 23 possessing low CSF folate levels and 19 of that subgroup also having the higher levels of autoantibodies (suggesting a connection between the autoantibodies and low folate levels in the CSF). Ramaekers II at 280-81.

Another article echoed the findings in Ramaekers II. Pet'rs' Ex. 50, Ref. 2 (Paolo Moretti, et al., *Brief Report: Autistic Symptoms, Developmental Regression, Mental Retardation, Epilepsy, and Dyskinesias in CNS Folate Deficiency*, 38 J. Autism Dev. Disord. 1170 (2008) ("Moretti")). The Moretti authors conducted assessments of seven children who had been diagnosed with a cerebral folate deficiency and determined that a "subset" of those manifesting developmental regression also had folate level abnormalities. Moretti at 1170. The studied sample, however, was not only facially small, but included four children who had "demonstrated neurological abnormalities in the neonatal period," and two whose neurologic impairments were so severe that they could not be assessed at all. *Id.* at 1171. The article observed an overlap between ASD symptoms and cerebral folate deficiency symptoms in five of the studied subjects and speculated that the blocking autoantibodies may have played a role in the manifestation of ASD symptoms, but that "their causative role remains to be determined." *Id.* at 1176.

Dr. Shafrir also cited R.E. Frye, et al., *Cerebral Folate Receptor Autoantibodies in Autism Spectrum Disorder*, 18 Molecular Psychiatry 369 (2013) ("Frye").[21] The Frye article purports to demonstrate a correlation between the level of receptor-blocking autoantibodies and lower levels of MTHF in the CSF in children who had not been diagnosed with a cerebral folate deficiency. Tr. at 137 (citing Frye at 6, Figure 2). The study specifically tested for the presence of blocking autoantibodies in 93 patients diagnosed with an ASD (a large subset of whom were patients of Dr.

[21] One of the Frye authors is Dr. Richard Frye – the same treater who first proposed that A.P.M. suffered from a cerebral folate deficiency. Tr. at 124.

Frye like A.P.M.). Frye at 372; Tr. at 135-36. Within the tested group, 56 patients were "positive" for the blocking autoantibodies – meaning they possessed them, although the majority of that subgroup possessed low levels of the antibodies at best. Frye at 372-73.

An alternative avenue of support Dr. Shafrir proposed for Petitioners' causation theory was the purportedly beneficial effects of treatments A.P.M. received after testing revealed the elevated folate receptor antibodies. According to Dr. Shafrir, the success of A.P.M.'s treatment with drugs (like leucovorin) containing folinic acid (along with the elimination of milk from his diet) corroborated his opinion that A.P.M. had a cerebral folate deficiency-like syndrome, by showing that reduction of the blocking effect of the autoantibodies was possible. Tr. at 109-10, 132, 139, 183, 202-03. He referenced studies showing that taking oral folinic acid supplements could rectify low CSF MTHF and lead to partial or complete clinical recovery. *Id*. at 122-26 (citing Ramaekers I). For example, Frye discussed the ameliorative effects of treating such children with leucovorin, although the article's authors admit that proof of the treatment's efficacy was anecdotally obtained from parent interviews rather than determined objectively. Frye at 371, 378 ("[t]his study was not a clinical trial").[22]

A significant deficiency in Dr. Shafrir's theory was the fact that – as he admitted – other than the elevated blocking antibody measurements, the medical records did not support the conclusion that A.P.M. had a cerebral folate deficiency of any kind. Thus, A.P.M. possessed none of the more severe symptoms of the subjects in Ramaekers I – something Dr. Shafrir conceded, and that even Dr. Frye before him had admitted. Tr. at 189; Pet'rs' Ex. 16 at 35. Indeed, Dr. Shafrir himself would not accept Dr. Frye's diagnosis that A.P.M. suffered from a cerebral folate deficiency, preferring instead to characterize it as an inadequately-studied "syndrome" – milder than a true cerebral folate deficiency, but still capable of producing developmental regression. Tr. at 103, 161 ("it hasn't been delineated yet"), 189-90, 204-05, 229 (citing Ramaekers I).

Dr. Shafrir similarly admitted that A.P.M.'s measured MTHF levels (as determined in his 2011 lumbar puncture) were within normal ranges. Tr. at 203-04. But he argued that the measured folate levels were more precisely characterized as "low normal" that (because the nature of cerebral folate deficiency was still not well understood) were nevertheless pathologic. *Id*. at 132. He also questioned the extent to which the CSF testing was reliable, noting that the medical records from

[22] Less than one week before the hearing, Petitioners filed additional literature suggesting that children who had experienced regression as part of their autism showed improvement after treatment with corticosteroids, thus attempting to further bulwark their contention that developmental regression can be the result of an autoimmune illness (since treatment focusing on suppressing the immune process is beneficial). Pet'rs' Ex. 70 (Frank H. Duffy, et al., *Corticosteroid Therapy in Regressive Autism: A Retrospective Study of Effects on the Frequency Modulated Auditory Evoked Response (FMAER), Language, and Behavior*, 14(70) BMC Neurol. 1471-2377 (2014)); Pet'rs' Ex. 71 (Sailaja Golla & John A. Sweeney, *Corticosteroid Therapy in Regressive Autism: Preliminary Findings from a Retrospective Study*, 12(79) BMC Med. 1741-7015 (2014)).

the lumbar puncture indicated that the tested CSF specimen was blood-tinged, thereby raising the possibility that the results were untrustworthy. *Id*. at 133, 205-06. Red blood cells, he reasoned, contain folic acid, and so the presence of red blood cells in the measured sample would alter the accuracy of the reading and artificially raise the reported level of MTHF. *Id*. at 449-52.

More broadly, Dr. Shafrir offered nothing, whether based on his own experience or a particular study, demonstrating or suggesting a link between *any* vaccine and the development of a cerebral folate deficiency, let alone the milder syndrome he was proposing as part of his opinion. He thus admitted that he was aware of no studies involving or suggesting that any vaccine may play a role in the production of the folate receptor blocking autoantibodies. Pet'rs' Ex. 50 at 32. At best, he proposed that since other vaccines have been shown to be associated with the development of other neurologic injuries caused by autoimmune processes, the same is possible here. Tr. at 147-48; Pet'rs' Ex. 53, Ref. 2 (M. Partinen, *Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland*, 7(3) PLoS ONE (Mar. 2012) ("Partinen")).

Partinen, for example, studied the widespread occurrence of narcolepsy after Finnish children received a particular formulation of influenza ("flu") vaccine. Partinen at 6. Dr. Shafrir proposed that Partinen demonstrated that a vaccine could cause a neurologic autoimmune-mediated disease, as well as the fact that the autoimmune process would occur in a progressive fashion akin to what A.P.M. allegedly experienced. Tr. at 147-48. He acknowledged, however, the many ways in which the Partinen study was inapposite, since (a) it involved a vaccine substantially different than the kind of flu vaccines administered elsewhere, including an adjuvant that was suspected to have played a role in the reaction, (b) genetic susceptibility to narcolepsy (perhaps even unique to Finland) had been proposed as an alternative causative factor, and (c) most importantly, Partinen did not even identify autoimmunity as the illness's mechanism. *Id.* at 152-55.

Dr. Shafrir's testimony also touched upon the impact of bovine milk consumption on the generation of the blocking autoantibodies. Dr. Shafrir admitted in his testimony that milk proteins had "up to 90 percent homology" with the folate receptors. Tr. at 185. This was consistent with Petitioners' literature. Ramaekers I at 1991. Indeed, another study, co-authored by Ramaekers and also submitted in support of Petitioners' causation theory, directly considers the relationship between milk and generation of the folate receptor-blocking autoantibodies. *See generally* Pet'rs' Ex. 50, Ref. 6 (V.T. Ramaekers, et al., *A Milk-Free Diet Downregulates Folate Receptor Autoimmunity in Cerebral Folate Deficiency Syndrome*, 50 Developmental Medicine & Child Neurology 346 (2008) ("Ramaekers III")). Ramaekers III found that re-introduction of milk to diets of children who previously had a cerebral folate deficiency caused their folate receptor blocking autoantibody titer to increase significantly. Dr. Shafrir thus maintained (consistent with

T.M.'s testimony) that *elimination* of milk from A.P.M.'s diet had the opposite effect, helping him to increase folate uptake (by reducing the production of autoantibodies). Tr. at 109-10, 139.

Even while testifying that milk played a defined role in the production of the blocking autoantibodies, however, Dr. Shafrir vigorously contested the notion that the blocking autoantibodies detected in A.P.M. in 2010 might have been the product of antigens contained in bovine milk (which T.M. admitted introducing to A.P.M.'s diet not long before he was 18 months old (*id.* at 72-73)), asserting that "if this was the cause [of A.P.M.'s autism] . . . then the entire children population in the world should be autistic," given widespread milk consumption. *Id*. at 110, 186. He further opined that it could not have happened in A.P.M.'s case in any event, because A.P.M. was exposed to some form of milk from birth (although this argument ignored the fact that A.P.M. had received bovine milk long before he was tested for the blocking autoantibodies in 2010). *Id*. at 185, 215-16.

Dr. Shafrir proposed that the timeframe between A.P.M.'s receipt of the DTaP vaccine and development of regressive/ASD-like symptoms (within three months of the vaccine's administration, or by the time A.P.M. was 18 months old) was medically acceptable. Tr. at 184; Pet'rs' Ex. 53 at 2; Pet'rs' Ex. 50 at 32. However, he acknowledged that the existing medical records did not permit him to propose precisely what that timeframe would be, or to cite instances from the medical record reflecting the course of the process. Tr. at 194. He averred that onset of A.P.M.'s developmental regression was even more difficult to pinpoint in this case because it was a "gradual process," without evidence of a sudden change in A.P.M.'s behavior (despite T.M.'s testimony that she did observe a dramatic change in the weeks immediately after the July 2006 vaccination). *Id*. at 102. He could conclude only that regression likely began before A.P.M. was 18 months old, given that T.M. had suggested that A.P.M. began to evince symptoms of developmental regression slightly before the 18-month well-child visit, and it was therefore reasonable to conclude she had observed such symptoms before records from that visit suggest. *Id*. at 194, 197-98.

Dr. Shafrir offered little beyond general medical literature directly supporting his arguments about the timeframe in which the autoimmune process leading to the production of the folate receptor-blocking autoantibodies would be expected to occur. *See, e.g.*, Agmon-Levin at 649. He instead relied on evidence involving other vaccines and other diseases to support the more general relationship between vaccines and autoimmunity and the timing of the autoimmune process. Thus, to counter Dr. Wiznitzer's claim that three to four months post-vaccination was too long for an autoimmune condition to develop, Dr. Shafrir pointed to an example in the Vaccine Table, which allows claims to proceed based on a timeframe of 42 days (or approximately a month and a half) for autoimmune conditions such as chronic arthritis after receipt of the MMR vaccine. Tr. at 146 (citing Pet'rs' Ex. 50, Ref. 5). He also pointed again to Partinen, which found a time

delay of several months between immunization and the subsequent narcolepsy. *Id*. at 143-45.[23] In light of such literature, he proposed that the latency period could be days, or even years, before onset manifested. *Id*. at 145.

C. Respondent's Expert – Dr. Wiznitzer

Dr. Wiznitzer graduated from the honors program in medical education at Northwestern University, where he received a bachelor's of science in medicine in 1975 and then his medical degree in 1977. Tr. at 236. He 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*. Dr. Wiznitzer currently works at Rainbow Babies and Children's Hospital in Cleveland, Ohio. *Id.* at 235. Dr. 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. Dr. Wiznitzer holds board certifications in pediatrics, neurology (with special qualification in child neurology), and neurodevelopmental disabilities. *Id.* at 237-40.

Dr. Wiznitzer has an active clinical practice, and he estimates that more than a quarter of the patients he sees weekly are individuals with autism (many of whom receive that diagnosis from him). Tr. at 238.[24] He also has ASD-related research and teaching experience. *Id*. at 239-40. When Dr. Wiznitzer started his current job at Rainbow Babies and Children's Hospital in 1986, he immediately got involved in autism research and has issued approximately 60 publications. *Id.* at 241. Additionally, Dr. Wiznitzer is on the Autism Subcommittee of the American Academy of Pediatrics and the American Academy of Neurology, both of which are working on new guidelines

[23] Dr. Shafrir also referenced these papers in support of an alternative causative mechanism – that the adjuvants contained in vaccines to stimulate their immunologic properties could play a role in the development of autoimmune diseases. Tr. at 152-53. However, he only brushed on the topic briefly, and adjuvant stimulation is not a central component of Petitioners' theory in this case. I note as well that theories relying on adjuvants to explain an adverse vaccine reaction have often been rejected by other special masters as unpersuasive in any event. *See, e.g.*, *D'Angiolini v. Sec'y of Health & Human Servs*., No. 99-578V, 2014 WL 1678145, at *57 (Fed. Cl. Spec. Mstr. Mar. 27, 2014), *mot. for review denied*, 122 Fed. Cl. 86 (2015), *aff'd*, No. 2015-5141, 2016 WL 1426294 (Fed. Cir. Apr. 12, 2016) (expert opinion that an adjuvant present in a vaccine could lead to an adverse reaction did not have sufficient scientific support to be a reliable basis for compensation in the Vaccine Program); *see also Snyder*, 2009 WL 332044 (thimerosal component of vaccines not shown to cause or contribute to development of autism).

[24] When he is in Cleveland, Dr. Wiznitzer normally sees patients at least seven half-days a week, and he also sees in-patients, on average, about two months out of the year. Tr. at 307, 309-10.

for the diagnosis and management of autism. *Id.* at 239-40. And he is also involved in teaching related to autism both at the medical center, as well as in the Cleveland area and nationally. *Id.* at 240.

Dr. Wiznitzer did not dispute that A.P.M. has an ASD,[25] but disagreed that the vaccines A.P.M. received on July 14, 2006, precipitated his development of autism. Tr. at 248-29, 265. In reaching this conclusion, Dr. Wiznitzer rejected Petitioners' assertion that A.P.M. has a cerebral folate deficiency, or that the anti-folate antibodies measured in A.P.M. caused his autism. *Id*. He also proposed that in fact it was the introduction of cow's milk in A.P.M.'s diet that was the more likely cause for his elevated levels of autoantibodies. *Id*. [26]

Dr. Wiznitzer questioned Dr. Frye's diagnosis of cerebral folate deficiency (as well as Dr. Shafrir's concurrent diagnosis that A.P.M. had some milder syndrome characterized primarily by the elevated blocking autoantibodies). First, he noted that A.P.M. was found to have normal levels of MTHF in his CSF, as Dr. Frye (as well as Dr. Shafrir) recognized. Tr. at 283, 288. Dr. Wiznitzer acknowledged the results may have been somewhat on the lower end of normal, but stressed that this had, in his opinion, no significance from a medical standpoint. *Id.* at 288, 438-39.

Second, Dr. Wiznitzer stressed that A.P.M.'s medical history did not reflect the typical clinical presentation of a child with cerebral folate deficiency, or any other neurodegenerative disorder for that matter. Tr. at 282, 287. Thus, A.P.M. had never experienced deceleration of head growth, poor vision, seizures, or other immediate intellectual impairment. *Id*. at 282-83, 360-61.

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[25] The term ASD encompasses a group of complex neurodevelopmental disorders characterized by "self-absorption, impairment in social interaction and communication, and a restricted range of activities and interests." *Dorland's* 180; *see also* Autism Spectrum Disorder Fact Sheet, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKES, Oct. 7, 2015, *available at* http://www.ninds.nih.gov/disorders/autism/detail_autism htm (last visited July 11, 2016); *see also* Resp't's Ex. C (Chris P. Johnson, et al., *Identification and Evaluation of Children with Autism Spectrum Disorders*, 120 Pediatrics 1183-1215 (2007) (noting that "ASDs are neurodevelopmental conditions with strong genetic underpinnings," and indicating that "[i]n addition to being a spectrum disorder, autism has a wide variability with respect to the presence and intensity of symptoms")). Children diagnosed with ASD are often reported by their parents to have displayed developmental or behavioral problems around 18 months of age, if not by the age of two, and a significant minority of children with ASD experience regression/loss of skills, including language or vocabulary. *Lehner v. Sec'y of Health & Human Servs*., No. 08-554V, 2015 WL 5443461, at *34-35 (Fed. Cl. Spec. Mstr. July 22, 2015) (discussing the diagnostic criteria and characteristics of ASDs). The parties largely did not contest the general scientific and medical understanding of ASDs.

[26] Although my decision includes review and discussion of Dr. Wiznitzer's primary testimonial points, I note that he has no more personal or professional expertise on the subjects of cerebral folate deficiency, immunology, or molecular biology that Dr. Shafrir, and therefore his opinions on medical and scientific topics ranging from the content of the DTaP vaccine and its protein sequences to the causes of the development of folate receptor blocking autoantibodies are subject to the same weighting concerns that I apply to Dr. Shafrir's testimony. Of course, because the Petitioners carry the initial burden of proof, and therefore must offer the proper expert to opine on the matters most relevant to their causation theory, the reliability of Dr. Shafrir's testimony was of primary importance.

Instead, Dr. Wiznitzer maintained that A.P.M.'s ASD development was consistent with one of the several ASD trajectories: autism with regression of skills manifesting during the second year of life. *Id.* at 260-66 (citing Resp't's Ex. D). Dr. Wiznitzer characterized such a temporal trajectory as common, with this type of clinical presentation occurring in approximately 10 to 15 percent of children diagnosed with ASD. *Id*. at 262. Dr. Wiznitzer concluded that A.P.M.'s autistic regression is of unknown etiology. *Id*. at 407-08.

A significant portion of Dr. Wiznitzer's testimony was devoted to rebutting Dr. Shafrir's assertions that the CSF testing results that indicated A.P.M. had "low normal" levels of folate were unreliable due to blood in the sample. Dr. Wiznitzer maintained that records from the procedure report pertaining to the CSF testing revealed that several CSF vials were collected, and that the first, purportedly bloody specimen would not have been the tested sample (out of the total amount collected). Tr. at 283-84, 367-71; *see also* Pet'rs' Ex. 16 at 10-11. He further maintained, drawing upon his experience in ordering similar tests and then reviewing the results, that a lab would not have run the MTHF level test on a visibly blood-tinged sample. *Id*. at 437-39.[27] He acknowledged, however, that the recorded test results did in one place characterize the red blood cell count as "high," but pointed out the notes from when the sample was drawn suggested any contaminated amount later cleared; he also proposed, based on his personal experience, that lab technicians would "spin [red blood cells] out" of a sample before testing (meaning subject the sample to a centrifuge to separate out serum portions to be tested). *Id.* at 371-74.

Dr. Wiznitzer also addressed Petitioners' arguments about the significance of A.P.M.'s elevated folate receptor-blocking autoantibodies. Although he did not dispute the accuracy of the testing results, Dr. Wiznitzer characterized them as no more than an "interesting finding" having little clinical importance – especially since they stood as the only lab results that even came close to suggesting A.P.M. had any kind of cerebral folate deficiency. Tr. at 301-02, 348. And even if A.P.M. was assumed to suffer from some lesser-understood syndrome evidenced by the presence of the folate receptor blocking autoantibodies, Dr. Wiznitzer denied that the DTaP vaccine could have caused the production of those antibodies, due to insufficient homology between the proteins in the vaccines and the folic acid receptor. *Id.* at 268. In that regard, he challenged whether a pentapeptide sequence – a five amino acid chain – was similar enough to a folate receptor protein chain to initiate the process needed to produce the blocking autoantibodies. *Id*. Instead, he proposed that a chain of at least 15 to 20 amino acids was necessary. *Id*. at 270-73 (citing Resp't's Exs. E and F), 303-09. Dr. Wiznitzer also offered evidence that Dr. Shafrir had referenced incorrect strains of components of the MMR and DTaP vaccines in arguing that either could potentially cause an autoimmune process via molecular mimicry. *Id.* at 307-310; 327-35. (As noted above, as

[27] Respondent filed several articles post-hearing supporting Dr. Wiznitzer's characterization of the cerebral spinal fluid testing procedures. Resp't's Exs. M-O.

a result of these arguments, Dr. Shafrir at hearing admitted that he could not establish homology for the MMR vaccine, and Petitioners dropped the MMR vaccine from their claim). Tr. at 443-44, 474; *see also* Post-Trial Brief at 19 n.5.

Dr. Wiznitzer characterized the scientifically-demonstrated homology between milk and proteins in the folate receptors (as also reflected in Petitioners' literature and expert testimony) as the "800-pound gorilla in the room," and therefore a more likely cause of A.P.M.'s heightened blocking autoantibody levels. Tr. at 272; 313; *see also* Ramaekers III. To that end, Dr. Wiznitzer presented evidence that there is 90 percent homology between the relevant peptide sequences in milk and the folate receptors in the brain – and thus molecular mimicry as the mechanism for the production of the blocking autoantibodies was far more plausible than what Dr. Shafrir proposed occurred with merely a five-protein homologous sequence. *Id*. at 315-16. Moreover, A.P.M. had previously been exposed to vaccines earlier in life with no similar alleged reaction, but had not been exposed to cow's milk prior to 18 months (around the time when A.P.M.'s language loss was first observed), further suggesting that milk had more likely generated the autoantibodies than the DTaP vaccine. *Id*. at 317.

Finally, Dr. Wiznitzer addressed the temporal relationship between receipt of the DTaP vaccine and onset of A.P.M's developmental symptoms. He argued that there was insufficient temporal proximity to link the vaccines received in July 2006, when A.P.M. was 15 months old, to the first description of regression at A.P.M.'s two year visit in April 2007, when "loss of language" was clearly described. Tr. at 279 (citing Pet'rs' Ex. 1 at 7). At best, three to four months passed between the vaccination and the earliest possible onset of regression in 2006 – too long in Dr. Wiznitzer's opinion for an autoimmune process to manifest. *Id*. at 280-81.

IV. APPLICABLE LEGAL STANDARDS

A. Petitioner's Overall Burden in Vaccine Program Cases

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[28]

[28] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121,

In this case, Petitioners do not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs*., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of

124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)), *appeal docketed*, No. 2015-5097 (Fed. Cir. June 19, 2015). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).[29]

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions

[29] There is ample contrary authority for the more straightforward proposition that the first *Althen* prong, like the overall test itself, simply applies a preponderance standard when evaluating if a reliable and plausible causal theory has been established. *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1350 (Fed. Cir. 2010). For purposes of the present analysis, I am stressing those cases focusing on the *plausibility* of the causal theory proposed, as opposed to whether preponderant evidence supports it, in order to avoid imposing on Petitioners a greater evidentiary burden than the law requires. This does not, however, change the fact that the theory's plausibility is properly analyzed by subjecting its components to the *Daubert* tests for scientific reliability. *Terran v. Sec'y of Health & Human Servs*., 195 F.3d 1302, 1316 (Fed. Cir. 1999).

against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dep't of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Testimony

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such a determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (*i.e*., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical

records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs*., 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms. It is equally unlikely that pediatric neurologists, who are trained in taking medical histories concerning the onset of neurologically significant symptoms, would consistently but erroneously report the onset of seizures a week after they in fact occurred").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneously medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir.), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human*

Servs., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of her own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

In determining whether a particular expert's testimony was reliable or credible, I may consider whether the expert offers an opinion that exceeds his training or competence. *Walton v. Sec'y of Health & Human Servs.*, No. 04-503V, 2007 WL 1467307, at *17-18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). While (in keeping with the liberality with which evidence offered in Vaccine Program cases is treated) I heard and have considered all of the testimony of the experts offered at the entitlement hearing, I may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See, e.g.*, *King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78-79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications). An opinion does not obtain legitimacy in the Program simply because it comes out of the mouth of a medical doctor – especially if that opinion concerns matters well outside the doctor's expertise.

D. Consideration of Medical Literature

Both parties filed medical and scientific literature in this case, including many articles (such as those discussing molecular mimicry and protein sequences in vaccines) that do not factor into the outcome of this decision. While I have reviewed all of the medical literature submitted in this case, I only discuss those articles that are most relevant to my determination and/or are central to Petitioners' case – just as I have not exhaustively discussed every individual medical record

filed. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. v. Sec'y of Health & Human Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to — and likely undermines — the conclusion that it was not considered").[30]

V. ANALYSIS

A. Petitioners Did Not Establish that A.P.M. Suffered from Any Form of Cerebral Folate Deficiency

Putting aside the allegedly causative role the DTaP vaccine played in A.P.M.'s regression, Petitioners' entire causation theory hinges upon acceptance of either Dr. Frye's diagnosis that A.P.M. suffered from a cerebral folate deficiency, or Dr. Shafrir's alternative proposal that A.P.M. suffered from some less-studied "syndrome" characterized by heightened levels of folate receptor blocking autoantibodies. Respondent squarely contests that A.P.M. had anything close to a cerebral folate deficiency. It therefore makes sense to consider at the outset whether Petitioners have successfully established in this case that A.P.M. suffered from any form of cerebral folate deficiency before evaluating whether the *Athen* test prongs have been satisfied. *Broekelschen*, 618 F.3d at 1346 (when an injury or diagnosis is disputed, and "the proposed injuries differ significantly in their pathology," the special master may "first find which of [the] diagnoses was best supported by the evidence presented in the record before applying the *Althen* test so that the

[30] In certain instances, Petitioners have emphasized, in their post-hearing filings, findings contained in literature either not offered as part of their main case, or buried within another document, and thus not highlighted for my attention as significant, contrary to the Pre-Hearing Order in this action. *See* Order, dated Dec. 18, 2014 (ECF No. 80) at 2 (setting deadline for submission of medical literature, directing parties to highlight significant portions thereof, and warning parties that "[a]bsent compelling circumstances, any exhibits not previously filed, nor timely filed and served by the date specified above, will not be admitted at the hearing").

Thus, Exhibit 72 (filed November 5, 2015) is a 102-page compendium of materials pulled from the website of an entity that apparently tests folate receptor blocking autoantibodies (offered in response to the question of whether the blocking antibody testing could be replicated, since here A.P.M. was only tested a single time). Hidden within that compendium is yet another Ramaekers-authored article – V.T. Ramaekers, et al., *Folinic Acid Treatment for Schizophrenia Associated With Folate Receptor Autoantibodies*, Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.10.002 ("Ramaekers IV"). Petitioners in their post-hearing briefing now address this article at length, suggesting that a "low normal" folate level measured in CSF can still be significant for purposes of determining if an individual suffers from a cerebral folate deficiency. Post-Hearing Brief at 24-26. I acknowledge that the point was referenced by Dr. Shafrir in his testimony (and in response to Dr. Wiznitzer's testimony about whether the blocking autoantibody testing conducted for A.P.M. could have been repeated (Tr. at 289)), and I have given it consideration in my decision. Nevertheless, it constitutes a piece of evidence that should have been identified *before* the hearing, since all parties understood that the significance of A.P.M.'s tested MTHF levels was disputed. I find the casual disregard with which Petitioners treated my Order on literature filed in this case to be inappropriate, and admonish counsel in the future to be more exacting in identifying literature his clients will rely on *in advance of hearing*.

special master could subsequently determine causation relative to the injury").

The parties do not dispute for the most part what constitutes a cerebral folate deficiency. Ramaekers I defines it as "any neuropsychiatric condition associated with low levels of [MTHF], the active folate metabolite in the [CSF]," in comparison with normal folate levels measured in blood serum. Ramaekers I at 1985; *see also* Ramaekers III at 346. The form of the condition with the most bearing on Petitioners' claim is infant-onset cerebral folate deficiency, a neurologic syndrome that commonly develops within four to six months after birth. Ramaekers I at 1985. This is because much of the literature offered by Petitioners for the core of their theory that a cerebral folate deficiency could result in autism involved children who were diagnosed with infant-onset cerebral folate deficiency. *See* Ramaekers I at 1985, 1987; Ramaekers II at 277; Ramaekers III at 346.

Infant-onset cerebral folate deficiency is characterized by "marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, . . . dyskinesias . . . ," and can in some cases (usually after the child is three years old) result in optic atrophy and blindness. Ramaekers I at 1985. Some children already diagnosed with this kind of infant-onset cerebral folate deficiency (and the severe symptoms outlines above) have also been found to display autistic symptoms as well, although no clear relationship has been drawn between children suffering from idiopathic autism and folate deficiency. Ramaekers III at 346; Moretti at 1175 ("these patients with CFD clearly differ in their neurological presentations and complexity from those with autism alone"). It is evident from both the literature filed in this case, as well as the testing benchmarks used to evaluate the significance of MTHF levels, that infant-onset cerebral folate deficiency offers the proper paradigm for reference in this case. *See, e.g.*, Pet'rs' Ex. 16 at 38.

There is also scientific support for the effect that blocking autoantibodies can have on the process of delivering folic acid to the brain (the relevant focus of analysis for present purposes). As Dr. Wiznitzer explained, the folate receptor acts as a "parking space" that transports folic acid from the blood to the central nervous system. Tr. at 287-88. Among other places in the body, these receptors are found on the surface of "epithelial cells on the choroid plexus"[31] – a network of blood vessels in the brain's ventricles that produces CSF. Ramaekers I at 1985; Tr. at 166. High levels of folate receptor-blocking autoantibodies can impede the transportation of folic acid into the central nervous system – evidenced by below-normal levels of MTHF levels in the CSF, in comparison to the amounts in the blood serum. Tr. at 287-88; Ramaekers I at 1985-86. This lack of folic acid in the central nervous system causes the symptoms associated with the infant-onset form of cerebral folate deficiency discussed in Petitioners' literature. Tr. at 287-88.

[31] The choroid plexus is the part of the brain that makes cerebrospinal fluid. *Dorland's* at 1463.

Despite the above, the evidence does not support Dr. Frye's cerebral folate deficiency diagnosis. A.P.M.'s MTHF levels were unquestionably within a normal range. Pet'rs' Ex. 16 at 22. In addition, and as Dr. Frye himself admitted, other than autism A.P.M. displayed none of the symptoms that would otherwise characterize infant-onset cerebral folate deficiency. *Id.* Even Dr. Shafrir could not accept Dr. Frye's diagnosis – a telling admission for a testifying expert. Tr. at 204 ("I just think we should reserve the term 'CFD' to the original description of the syndrome . . . and if we stick to it, [A.P.M.] did not have CFD. He just has autism"). Certainly I am not bound to accept Dr. Frye's diagnosis merely because he was one of A.P.M.'s treaters – especially in light of more persuasive contrary evidence. *Snyder*, 88 Fed. Cl. at 746 n.67. At bottom, Petitioners placed inordinate weight on the very fact that A.P.M. had a developmental problem as proof of its purported cause (cerebral folate deficiency) (Tr. at 96, 100, 103-105), even though this component for the diagnosis stood alone, without evidence of any of the other clinical criteria relevant to a cerebral folate deficiency diagnosis.

Petitioners' arguments to the contrary were unpersuasive. For example, Petitioners attempted to cast doubt on the reliability of A.P.M.'s CSF tests, asserting that the sample tested was contaminated by red blood cells that resulted in a false-normal reading. Yet the medical records filed in the case strongly suggest that *multiple* samples of A.P.M.'s CSF were taken at one time, thereby making it likely that the CSF folate measurements were not thrown off by a single poor sample. Pet'rs' Ex. 16 at 10-11**.** Those records further note that the lab technicians themselves were aware of the problem with the purportedly tainted sample (Pet'rs' Ex. 16 at 10 ("CSF was *initially slightly* blood-tinged but cleared") (emphasis added)), allowing the reasonable inference that had the sample truly been contaminated, it would not have been tested. And the procedure was deemed successful when the sample was drawn, further bulwarking the test's reliability. Pet'rs' Ex. 6 at 11. Dr. Wiznitzer also convincingly testified (based upon his own clinical experience with lumbar puncture procedures and bulwarked by documentary evidence) that a lab would not test a contaminated sample, or would separate the constituent elements in the CSF before testing. Tr. at 439. The weight of the evidence supports the conclusion that A.P.M.'s CSF folate test results are reliable.

Petitioners also argued (amplified in their post-hearing filings) that "a finding of low normal folate levels in the [CSF] of patients does not operate to exclude or vitiate the diagnosis of cerebral folate deficiency, especially when other factors are present." Post-Hearing Brief at 26 (citing V.T. Ramaekers, et al., *Folinic Acid Treatment for Schizophrenia Associated With Folate Receptor Autoantibodies*, Mol. Genet. Metab. (2014), http://dx.doi.org/10.1016/j.ymgme.2014.10.002 ("Ramaekers IV")). But Dr. Shafrir failed to reliably or persuasively explain why a low normal reading could still be significant, especially since he personally lacked the expertise to interpret the significance of a lower normal result. His other testimony disputing Dr. Frye's conclusion (which simply accepts the CSF test results as

accurate and does not qualify the meaning of a low normal result) that A.P.M. even had a cerebral folate deficiency, given the lack of other corroborative evidence, also undermines his "low normal" argument.

Ramaekers IV itself does not aid Petitioners' argument. Ramaekers IV involved testing for CSF folate levels and the presence of the folate receptor blocking autoantibodies in 18 patients, all of whom were older than A.P.M. and all of whom were diagnosed with schizophrenia – a condition not comparable to A.P.M.'s ASD beyond its general neurologic underpinnings. Ramaekers IV; Pet'rs' Ex. 72 at 96-98. Putting aside that such factors immediately highlight the danger of overstating the article's relevance herein, the larger problem is that Ramaekers IV did not focus at all on the significance of a low normal folate reading in the CSF. Instead, Ramaekers IV concerned itself (in part) with the *relationship* that the blocking autoantibodies have to the levels of folate measured in the CSF, as fluctuating levels of the antibodies can change how much folate is transported to the brain over time (and subsequently reflected in CSF testing). Even on that topic, the article was somewhat inconclusive. Ramaekers IV (Pet'rs' Ex. 72 at 100 ("our data do not suggest a close correlation between the titer of FRα antibodies and CSF MTHF values at the time of the spinal tap, [but] it may well be that CSF MTHF concentrations reflect the cumulative result of blocked MTHF transfer taking place during the days or weeks prior to the spinal tap")). Here, other than the "low normal" folate levels, there is no evidence of fluctuation of blocking autoantibodies, and Petitioners did not otherwise establish what A.P.M.'s levels were at the time of his vaccinations (which occurred four years before the autoantibody testing). Petitioners are thus left with a normal folate reading, which rebuts their claim that A.P.M. suffered from a cerebral folate deficiency.

Petitioners' fallback argument – that the elevated levels of blocking autoantibodies as determined in 2010 suggest that A.P.M. suffered from some milder, less-understood form of cerebral folate deficiency – fares no better. As a threshold matter, Dr. Shafrir's affirmation of the existence of such a clinically-significant syndrome is unsupported by any filed medical or scientific literature. No evidence was offered showing that a child who did not suffer from an infant-onset kind of cerebral folate deficiency, like A.P.M., might nevertheless experience developmental regression simply because the child displayed heightened levels of the blocking autoantibodies, without any other indicia of a cerebral folate deficiency beyond autism. Instead, the filed literature all involved patients with a clear, agreed-upon cerebral folate deficiency diagnosis, established by evidence of clinical factors lacking for A.P.M.

Ramaekers I, for example – the piece of literature most cited in this action – involved a study of 28 children much younger than A.P.M. at the time of vaccination, none of whom were shown to have been vaccinated first, but all of whom were diagnosed with infant-onset cerebral folate deficiency, based on obvious clinical criteria which they had displayed in the months after

birth – unlike A.P.M., who had no such symptoms even at 18 months of age, when his language loss is alleged to have begun. Ramaekers I at 1986-87. Thus, although Ramaekers I did determine that the studied children possessed heightened levels of the blocking autoantibody, and proposed that the presence of those autoantibodies might have significance, its studied sample would not have included A.P.M., as Dr. Shafrir readily admitted. Tr. at 212. As a result, any association Ramaekers I drew between possession of a heightened level of the autoantibodies and development of cerebral folate deficiency cannot be reasonably applied to A.P.M.

The other literature was similarly unsupportive of Dr. Shafrir's proposal of the existence of a blocking autoantibodies syndrome. In each instance, the studied patients found to possess heightened levels of the antibodies were unquestionably suffering from infant-onset cerebral folate deficiency, presenting with a number of symptoms far more severe than what A.P.M. experienced. The only article that comes close to evaluating the matter from the other end of the spectrum (the impact of the presence of the autoantibodies and their relationship to autism) is Frye, which at best (and based, by the authors' own admission, on a biased sample[32]) finds some association between children with an ASD and the presence of the autoantibodies, without considering the autoantibodies' causal role, or even what produced them in the first place. Frye at 378.

Arguments that A.P.M.'s allegedly successful folinic acid treatments established indirectly that he likely suffered from some form of cerebral folate deficiency were similarly unpersuasive. Post-Trial Brief at 30-31. The claims of A.P.M.'s improvement as a result of the treatments were largely anecdotal, coming mostly from T.M. & R.R.M themselves, or were mainly linked to the elimination of milk from his diet. Tr. at 139-40. Respondent, by contrast, pointed to record evidence (in particular, language and communication assessments by trained developmental professionals performed on A.P.M. in 2011) that suggested *no* dramatic improvements of the kind claimed by Petitioners. Tr. at 295-97 (citing Resp't's Ex. A at 110 (Dr. Wiznitzer's expert report, in which he opines that the rapid improvements T.M. reported A.P.M. having experienced after beginning to take folinic acid are contradicted by notations in the contemporaneous medical records)). The Petitioners otherwise could offer no additional autoantibody testing results to quantify the level of autoantibodies after A.P.M.'s treatments or corroborate their purported ameliorative effects. And (as discussed below), it is just as likely (to the extent the autoantibodies were in fact causing A.P.M.'s developmental problems) that the milk reduction was the reason for their diminishment. Thus, the purported benefits of these treatments are too subjective, and their results too uncertain, to constitute reliable proof that A.P.M. in fact suffered from a cerebral folate deficiency, especially given the strong evidence (such as normal folate levels and lack of severe

[32] The children tested for the presence of the autoantibodies in Frye were, like A.P.M., being treated by doctors like Dr. Frye who were actively exploring the relationship between cerebral folate deficiency and autism, and were even tested at the same SUNY Downstate lab that tested A.P.M. Frye at 370. Frye's authors thus admitted that the test was potentially subject to "referral bias." Frye at 378.

symptoms) going the other direction.

Beyond all of the above, the determination (treated by Petitioners as unassailable) that A.P.M.'s blocking autoantibody levels were "very high" (Post-Trial Brief at 8-9) is *itself* an unreliable basis for Petitioners' theory. A single test – performed in October 2010, more than four years after the July 2006 DTaP vaccination – is the sole evidence offered for this conclusion, but its temporal remoteness from the date of vaccination is enough to call into question the implication of its findings. In effect, Petitioners are proposing that an autoimmune process initiated in 2006 was sufficiently robust and persistent to be measurable in a clinically significant manner four years later. Yet, at the same time (and in their effort to defend the meaningful nature of the "low normal" MTHF measurements from A.P.M.'s lumbar puncture), Petitioners also argue that folate levels fluctuate as autoantibody levels change. Post-Trial Brief at 24-26; Tr. at 458-60 ("the important thing, they showed dramatic fluctuation in the level of the antibodies"). If so, then how can a 2010 test ever reveal what autoantibody levels were four years before, and whether the levels were at that time sufficiently high to be pathologic? Moreover, the autoantibody test results were just outside the moderate range, rather than facially high in the manner emphasized by Petitioners. To the extent the results were later characterized as alarmingly high by Dr. Frye, the record clearly establishes that he did so in error (confusing a 1.19 titer level for 1.9) (*compare* Pet'rs' Ex. 16 at 38 *with* Pet'rs' Ex. 16 at 35).[33]

B. Petitioners Did Not Adequately Rebut Evidence That Bovine Milk Can Promote Blocking Autoantibodies

Petitioners sought to bulwark their argument about the role the blocking autoantibodies played in A.P.M.'s developmental regression with assertions about the effectiveness of treatments intended to reduce the antibodies, such as medicines containing folinic acid, or diet alterations to eliminate bovine milk. But in so doing, they highlighted Respondent's arguments that bovine milk could also have contributed to A.P.M.'s elevated blocking antibody titer levels.

The single piece of medical literature most relied upon by Petitioners in this case, Ramaekers I, clearly acknowledges a relationship between bovine milk and the production of the blocking autoantibodies. Ramaekers I at 1991. Ramaekers III goes on to explicitly evaluate that relationship, exploring the impact of the reduction of bovine milk consumption on the antibody levels. Ramaekers III at 346 ("[i]n the CFD syndrome, the clinical manifestations typically occur after the switch to bovine milk"). It was also undisputed that the homology between certain bovine

[33] In addition, although Dr. Frye did not testify at trial, there are other discrepancies in his characterization of testing results (such as his later inflation of the "low normal" folate levels reflected in A.P.M.'s CSF testing as actually "below" normal) that lead me to question the overall reliability of some of the conclusions he reached. Pet'rs' Ex. 14 at 3; Pet'rs' Ex. 46 at 1. The fact that he was literally one of A.P.M.'s "treaters" (albeit four years after the vaccination in question) is reasonably weighed against medical record evidence undercutting his assertions.

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. Tr. at 185, 314-16. Because Petitioners rely on a five-peptide sequence to argue molecular mimicry was sufficient to cause an autoimmune reaction to the DTaP vaccine, they cannot credibly dispute that even *greater* homology between milk proteins and the folate receptors would not have at least the same effect.

In addition, the facts of this case are not inconsistent with the proposition that bovine milk might have contributed to A.P.M.'s receptor-blocking autoantibody levels. T.M.'s testimony established that she began feeding A.P.M. with bovine milk within months after he received the DTaP vaccine in 2006. Tr. at 72-73. Removing milk from A.P.M.'s diet purportedly resulted in improvement in his development and related behavior. *Id.* at 470-48, 109. And the four-year lag between when A.P.M.'s autism is alleged to have begun and the date of the autoantibody testing further allows for the possibility that milk consumption in the intervening time period had something to do with A.P.M.'s autoantibody levels.

In response to such persuasive evidence, Dr. Shafrir simply offered sweeping denials. He argued that if bovine milk did in fact play a role in the blocking autoantibody production, A.P.M. should have had problems long before his regression symptoms actually manifested (since he was breast-fed from birth) (Tr. at 185-86), or more globally that *all* children fed bovine milk should be autistic. *Id.* at 110; Reply at 11. But such arguments only highlight the weakness of Petitioners' theory, which invests heavily in the concept that the presence of high levels of autoantibodies for A.P.M. is significant. If Petitioners' argument that the DTaP vaccine could possibly cause an increase in the production of the autoantibodies sufficient to trigger a developmental regression is accepted, then how can *more* scientifically-reliable evidence – evidence cited by Petitioners themselves – that milk plausibly causes the production of those autoantibodies be rejected as preposterous?[34]

To be sure – I am not determining in this case that Respondent has established bovine milk as an alternative cause of A.P.M.'s elevated blocking autoantibody levels, as measured in October 2010. The evidence does not permit that conclusion, nor have I found that Petitioners carried their prima facie case sufficiently to shift the burden to Respondent. *Gerhardt v. Sec'y of Health &*

[34] Petitioners' shrugging off the science linking bovine milk to the blocking autoantibodies is also contrary to the very legal standards applicable herein. It is well-recognized in the Vaccine Program that, "in a field bereft of complete and direct proof of how vaccines affect the human body" (*Althen*, 418 F.3d at 1280), claimants seek to prove something that is inherently uncommon – an adverse reaction to a vaccine sufficient to cause significant injury – and for this reason, petitioners are allowed to rely on circumstantial evidence, not required to submit epidemiologic proof of a vaccine's capacity for harm, etc. Yet in this case, Petitioners attempt to turn that presumption on its head, arguing that an otherwise scientifically-reliable explanation for the role of bovine milk in the production of the blocking autoantibodies must be rejected because its purported effects (autism) are insufficiently *common*.

Human Servs., No. 9-180V, 2014 WL 4712690, at *8 (Fed. Cl. Spec. Mstr. Aug. 29, 2014) (once a petitioner has satisfied the three prongs of *Althen*, "the burden shifts to the Respondent to demonstrate by preponderant evidence that the petitioner's injury is 'due to factors unrelated to the administration of the vaccine'"). But it is well-recognized that Respondent may offer evidence, or point to existing evidence in the record, that contradicts or weakens a petitioner's evidence, and in so doing demonstrate that the petitioner cannot meet her overall burden, without the burden of proof ever shifting. *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[o]ur decisions support the commonsense proposition that evidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question"); *La Londe v. Sec'y of Health & Human Servs.*, 110 Fed. Cl. 184, 198 (2013) ("[r]egardless of whether the burden ever shifts to the respondent, the special master may consider the evidence presented by the respondent" when determining if petitioner's initial burden has been met), *aff'd*, 736 F.3d 1334 (Fed. Cir. 2014). Respondent has done so here, but Petitioners have failed to persuasively address that showing.

C. Petitioners Have not Satisfied the Althen Prongs

Petitioners' case heavily relied upon the finding that A.P.M. suffered from cerebral folate deficiency or some milder variant, so my contrary conclusions are fatal to their claim. Yet review of the three *Althen* prongs for establishing Non-Table causation reveals that Petitioners also would not be able to prevail on their claim due to other evidentiary failures.

1. Petitioners did not Establish a Reliable and Plausible Causation Theory

Highly relevant to my analysis is Dr. Shafrir's lack of expertise on the topics most relevant to Petitioners' causation theory. Dr. Shafrir has competence to testify on a variety of neurological conditions, including autism itself, and to draw upon his experience in proposing possible causes for a child's developmental regression based on the case's record. But by his own admission, he has no personal experience in studying or diagnosing cerebral folate deficiencies, or how the conditions might relate to autism, and thus his testimony largely tracked the scientific or medical literature offered by Petitioners and was otherwise speculative. Tr. at 228. This greatly diminished the evidentiary value of the opinions he offered in this action and the resulting weight I gave them.[35] *Murfam Farms, LLC ex rel. Murphy v. United States*, No. 06-245T, 2008 WL 4725468, at

[35] Notably, this case is not the first time Dr. Shafrir has provided expert testimony in support of the claim that a child's autism was vaccine-caused, based on the concept that the vaccine precipitated an autoimmune condition. Never, however, has he been found to be persuasive in so doing, and his expertise on the subject has repeatedly been called into question. *See, e.g., R.V. & E.V., parents & natural guardians of L.V., a minor v. Sec'y of Health & Human Servs.*, No. 08-504V, 2016 WL 3882519 (Fed. Cl. Spec. Mstr. Feb. 19, 2016), *mot. for review den'd*, 127 Fed. Cl. 136 (2016), *appeal docketed*, No. 16-2400 (Fed. Cir. July 29, 2016); *R.K. on behalf of A.K. v. Sec'y of Health & Human Servs.*,

*1 (Fed. Cl. Sept. 19, 2008) ("[u]nder *Daubert* . . . , reliable expert testimony is grounded in the methods and procedures of scientific, technical, or specialized knowledge in the expert's discipline, and is not merely subjective belief or unsupported speculation").

Beyond such expert issues, however, the substance of Petitioners' medical theory was itself unreliable on several levels. Overall, T.M. & R.R.M proposed that a child could develop some form of cerebral folate deficiency after receiving the DTaP vaccine and that the deficiency in turn would produce autistic regression. At least one link in their theory's chain – the relationship between folate levels in the CSF and the presence of blocking autoantibodies – was supported by reasonable medical literature, as demonstrated by the Ramaekers series of articles, although these studies largely involved children with symptoms far more closely associated with the condition than anything A.P.M. displayed, limiting the overall weight associated by establishing the existence of this relationship.

From there, however, Petitioners' theory weakens considerably. In particular, Petitioners lacked reliable and persuasive medical or scientific literature demonstrating a link between the DTaP vaccine and the production of the blocking autoantibodies. Instead, Petitioners relied on studies involving other vaccines and other illnesses, for the circumstantial proposition that because vaccines can be linked to autoimmune conditions, the same occurred here. But the support offered for the proposition was too attenuated, involving different vaccines, different illnesses, or different circumstances. Partinen, for example, not only involved a different vaccine and injury (narcolepsy), but also occurred in circumstances (admitted by Dr. Shafrir) where the vaccine's adjuvant was more likely than not the cause of the injury, or some genetic susceptibility specific to the study subjects. Partinen at 7-8; Tr. at 141-45. Articles such as Agmon-Levin were simply too broad in focus to constitute persuasive support for the theory offered in this case; simply because other vaccines have been linked to autoimmune conditions does not mean the same can be concluded to have occurred *in this case*.

The same deficiencies characterize the scientific support offered by Petitioners to suggest a relationship between autism and cerebral folate deficiency. Articles like Moretti were insufficiently powered to constitute reliable support for this part of the theory, given the seven-subject sample size – not to mention the fact that a majority of the studied children displayed symptoms produced by infant-onset cerebral folate deficiency that the parties agree were never experienced by A.P.M. Moretti at 1171, 1176. The Frye article suffered from sample bias (given that so many of the tested children were already receiving treatment from Dr. Frye himself as well

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No. 03-0632V, 2015 WL 10936124 (Fed. Cl. Spec. Mstr. Sept, 28, 2015), *mot. for review den'd*, 125 Fed. Cl. 57 (2016), *appeal docketed*, No. 16-1609 (Fed. Cir. Feb. 23, 2016); *see also Wright v. Sec'y of Health & Human Servs.*, No. 12-423V, 2015 WL 6665600, at *2 (Fed. Cl. Spec. Mstr. Sept. 21, 2015) (characterizing causation opinion offered by Dr. Shafrir that child had experienced autoimmune encephalitis resulting in regression as "highly speculative, unsupported, and completely unpersuasive").

as like-minded treaters), and lacked a reasonable control group to gauge autoantibody levels in children that did not suffer from an ASD. Frye at 371, 378. To the extent Petitioners relied upon Frye because its reporting of the allegedly successful results of folinic acid treatment also suggests (from a different angle) a relationship between autism and folate deficiency, the evidence of such positive results was subjective, derived entirely from parental reports, and therefore insufficiently reliable from a scientific standpoint.

The topic of molecular mimicry well illustrates the nature of Petitioners' failure to carry their overall causation theory burden. Proof of a mechanism by which a vaccine causes illness is not necessary to establish a plausible scientific theory under the first *Althen* prong. *Andreu*, 569 F.3d at 1378-79; *Knudsen,* 35 F.3d at 551. Petitioners nevertheless devoted a great deal of hearing time to presenting evidence intended to prove homology between components of the DTaP and MMR vaccines and human proteins in the folate receptor cites. Tr. at 166-69; Post-Trial Brief at 19-24.[36] In so doing, however, they relied on the testimony of an expert who not only lacked direct experience on the topic, but who made a mistake about homology involving one of the relevant vaccines (the MMR) that was significant enough to cause Petitioners to abandon the MMR vaccine entirely at trial as a basis for their claim. Post-Trial Brief at 19 n.5.

Petitioners' contradictory position on bovine milk's role in the generation of the blocking autoantibodies is glaring as well. Petitioners ask for a finding that a five-protein sequence common to pertussis and the folate receptor sites was sufficiently homologous to initiate an autoimmune process, while questioning evidence suggesting bovine milk's role in the generation of those same autoantibodies, based on an even greater demonstrated homology between protein sequences in bovine milk and the folate receptors in the body. *See generally* Ramaekers III. And at the same time, Petitioners also highlighted the allegedly salutary impact of removing milk from A.P.M.'s diet.

In defending their causation theory, Petitioners shield themselves behind the more lenient evidentiary standards in the Program (specifically in relation to *Althen* prong one) that, they correctly state, do not require scientific certainty. Post-Trial Brief at 20, 32 (citing *Althen*, 418 F.3d at 1280). Here, however, the evidence offered by Petitioners is notably weak in important respects, failing to link those components of the theory that have somewhat more reliability or narrower points. It was the failure of certain integral components of the theory that compel the determination

[36] In their defense, Petitioners explained that they invested efforts in establishing the mechanism underlying their theory in order to burnish the theory's reliability overall. Post-Trial Brief at 20. Such efforts were misplaced, however – for even if I accepted that sufficient homology existed for an autoimmune reaction to have theoretically occurred, I would still find that the theory was unreliable for other reasons, given (a) a lack of evidence linking *any* vaccine to production of the blocking autoantibodies, and (b) a lack of persuasive evidence linking the presence of the autoantibodies (without other symptoms of cerebral folate deficiency) to the development of an ASD.

that the theory overall lacks plausibility and/or is unreliable from a scientific standpoint.

My conclusions herein do not occur in a vacuum, but are properly informed by the similarities between Petitioners' theory in this case and those of the many claimants who have gone before. Since the resolution of the OAP cases, there have been numerous petitions attempting to establish that a variety of vaccines cause autism or an ASD. *See, e.g., Hardy v. Sec'y of Health & Human Servs.*, No. 08-108V, 2015 WL 7732603, at *4-5 (Fed. Cl. Spec. Mstr. Nov. 3, 2015) (petitioners failed to demonstrate that DTaP vaccine caused or significantly aggravated underlying mitochondrial disease resulting in ASD); *Miller v. Sec'y of Health & Human Servs.*, No. 02-235V, 2015 WL 5456093 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (petitioners failed to demonstrate that several childhood vaccines caused encephalopathy or aggravated underlying mitochondrial disease/dysfunction); *Lehner*, 2015 WL 5443461 (petitioners failed to demonstrate that flu vaccine resulted in autoimmune encephalitis). As Special Master Hastings noted in the recent *Hardy* decision, however, to date *every* post-OAP Non-Table claim seeking compensation for autism injuries purportedly related to a vaccine that has been tried has failed. *Hardy*, 2015 WL 7732603, at *4-5 (referencing eleven autism claims unsuccessfully tried (including *Miller* and *Lehner*), plus six that were rejected (over the petitioners' objections) without trial). In particular, theories that a vaccine provoked an autoimmune reaction resulting in developmental problems have also failed repeatedly. *See, e.g., R.V. & E.V., parents & natural guardians of L.V., a minor v. Sec'y of Health & Human Servs.*, No. 08-504V, 2016 WL 3882519 (Fed. Cl. Spec. Mstr. Feb. 19, 2016), *mot. for review den'd.*, 127 Fed. Cl. 136 (2016), *appeal docketed*, No. 16-2400 (Fed. Cir. July 29, 2016); *R.K. on behalf of A.K. v. Sec'y of Health & Human Servs.*, No. 03-0632V, 2015 WL 10936124 (Fed. Cl. Spec. Mstr. Sept, 28, 2015), *mot. for review den'd*, 125 Fed. Cl. 57 (2016), *appeal docketed*, No. 16-1609 (Fed. Cir. Feb. 23, 2016). This case is no different.

2. The DTaP Vaccine Did Not Cause A.P.M.'s Regression.

The medical records suggest other weaknesses in Petitioners' proof that support my conclusion that they have not shown by a preponderance that the DTaP vaccine caused A.P.M.'s developmental symptoms and ASD.

In particular, the record does not establish that A.P.M. experienced a reaction to the vaccine sufficient to suggest he was undergoing an autoimmune process. All Petitioners could point to were his initial regression symptoms – but they occurred (at the earliest) three months from the July 2006 vaccination, with little to no prior temporal hints that A.P.M. was experiencing any reaction to the DTaP vaccine. Thus, even if I credit T.M.'s assertions (corroborated somewhat by records establishing phone calls) that she contacted A.P.M.'s pediatrician to report a post-vaccination reaction she witnessed within the weeks immediately after the vaccination, the record is devoid of evidence that A.P.M.'s symptoms were more than a transient reaction to the vaccines

he received, rather than the start of some progressive autoimmune process sufficient to create the blocking autoantibodies. Indeed, those autoantibodies were not measured until four years after vaccination, and Petitioners provided no persuasive evidence explaining why such testing could reliably predict what the autoantibody levels would have been when A.P.M. was 15-months old. The overall record more persuasively suggests that any loss of skills A.P.M. experienced was consistent with idiopathic autism, as proposed by Dr. Wiznitzer. Tr. at 265-66, 349.[37]

The post-vaccination months are especially telling in this respect, for they suggest A.P.M.'s regression may have begun even later than that alleged by Petitioners. There is complete medical record "radio silence" between the July 2006 date of A.P.M.'s DTaP vaccination and the next well-child visit in October of that year – an absence of any suggestion that the vaccine was causing a significant physiologic change in A.P.M. In addition, the record from that October visit alludes only tangentially to a speech problem (in comparison to the subsequent record from April 2007). *Compare* Pet'rs' Ex. 21 at 32 (October 18, 2006, visit where listed as "very healthy") *with* Pet'rs' Ex. 1 at 7, 36 (April 14, 2007, visit documenting concerns regarding A.P.M.'s development resulting in a referral to a specialist). Indeed, the bulk of the record evidence revealing T.M. & R.R.M' dawning awareness of A.P.M.'s regression was generated some time *after* the 18-month visit, suggesting an even longer period of time had passed – but with no demonstrable reaction that could serve as a persuasive link between the vaccination and the regression itself. This is too long a period (especially given the lack of a persuasive theory) to find that any reaction to the DTaP vaccine was causally-related.

[37] For purposes of comparison, it is instructive to consider the facts of two of the only cases where the petitioners have successfully established entitlement based on the argument that a vaccine reaction precipitated ASD-like symptoms. While both cases involve Table claims (and therefore where causation was not at issue), they still provide some example of the kind of evidence of severity that would be present if a child were in fact experiencing a reaction sufficient to produce a developmental regression.

In *Poling v. Sec'y of Health & Human Servs.*, No. 021466V, 2011 WL 678559 at *1 (Fed. Cl. Spec. Mstr. Jan. 28, 2011), for example, the child in question (who was later diagnosed with a mitochondrial disease) had received several vaccinations (including MMR), and then *within 48 hours* developed a high fever that became low-grade over the next several days, along with inconsolable crying, sleeplessness, and significant, noticeable motor problems that worsened over the next several days. *See R.V. & E.V., parents & natural guardians of L.V., a minor v. Sec'y of Health & Human Servs.*, No. 08-504V, 2016 WL 3882519 at *36 (Fed. Cl. Feb. 19, 2016), *review denied, decision aff'd sub nom. R.V. v. Sec'y of Health & Human Servs.*, 127 Fed. Cl. 136 (2016). More recently, in *Wright v. Sec'y of Health & Human Servs.*, No. 12-423V, 2015 WL 6665600 (Fed. Cl. Spec. Mstr. Sept. 21, 2015) a child was proven, by a meticulous factual showing, to have received Pentacel (a multi-virus vaccine), and then, on the drive home from the pediatric visit at which the vaccination was administered, experienced a brief seizure, followed by a week in which he displayed a decreased level of consciousness and lethargy, during which the child's parents made many unsuccessful efforts to convince his pediatric treaters of the severity of his condition. *Wright*, 2015 WL 6665600, at *12-16.

3. Petitioners did not Establish a Medically Reasonable Timeframe

Petitioners appear to have conceded to some degree that they cannot propose either a precise timeframe in which the autoimmune process leading to the production of blocking autoantibodies should take place, or a timeframe in which the process *in this case* occurred. Thus, Dr. Shafrir's own expert report stated that the timeframe is "simply not known" (Pet'rs' Ex. 53 at 2), and he reiterated that admission at trial. Tr. at 182-84.

Petitioners' post-trial brief nevertheless asserts that this third *Althen* prong was met, but relies on conclusory reasoning for this point. Thus, they argue that because A.P.M. displayed initial symptoms of a developmental regression around three months after vaccination, it logically took that long for the process to work. Post-Trial Brief at 37-38; Reply at 2-5. As already noted, however, Petitioners were unable to offer a reliable, plausible causation theory supporting their claim – including how long the process of production of the blocking autoantibodies would be expected to take. They also did not offer any literature that would shed light on how long it would actually take to inhibit folate transport to the brain[38] sufficient to cause the developmental regression seen with A.P.M.

At most, Petitioners offered articles such as Agmon-Levin, which makes the sweeping statement that "the latency period between vaccination and autoimmunity ranges from days to years" (Agmon-Levin at 648) – an all-inclusive timeframe that is entirely too broad to satisfy this *Althen* prong. *Pafford v. Sec'y of Health and Human Servs*., 451 F.3d 1352, 1358 (Fed. Cir. 2006) ("[w]ithout some evidence of temporal linkage, the vaccination might receive blame for events that occur weeks, months, or years outside of the time in which scientific or epidemiological evidence would expect an onset of harm"). Or they relied on the fact that there exist Table claims permitting petitioners to establish entitlement based on evidence of autoimmune processes occurring in shorter time periods (Tr. at 146) – even though the fact that such claims are actionable cannot stand as proof in a Non-Table claim of what is "medically acceptable" *under these circumstances.*

Program petitioners cannot satisfy the third *Althen* prong by reflexively arguing that the actual span of time (reflected in the medical record) between vaccination and onset of illness automatically establishes a "medically acceptable" timeframe. *Koehn v. Sec'y of Health & Human Servs*., 773 F.3d 1239, 1244 (Fed. Cir. 2014) (characterizing expert opinion that the "time for developing sufficient antibodies for immunity after receiving a vaccine is always consistent with

[38] Dr. Shafrir admitted at hearing that not all folate receptors are located in the brain or are necessary for folate transport (which he termed "redundancy"), and therefore the loss in function of many receptors would have no causal relationship to the developmental symptoms at issue in this case. Tr. at 145.

injury from the vaccine" as "a proposition that, without any evidentiary support, we simply cannot accept"). But that is plainly the Petitioners' position in this case.

CONCLUSION

After review of the record in this case and having heard T.M.'s testimony, I can easily conclude that T.M. & R.R.M are loving parents and have done all they can to care for A.P.M. and treat his autism. I also have no reason to doubt their sincerity in pursuing this claim. But the factual record simply does not support their contention that the DTaP-Hib vaccine had any connection to A.P.M.'s developmental regression and ASD diagnosis, nor have the Petitioners established that the vaccine *could* result in that kind of regression in the manner proposed by their theory, given its heavy reliance of establishing that A.P.M. suffered from a mild form of cerebral folate deficiency. There is no more than a temporal relationship between vaccination and regression – not nearly enough to satisfy the Act's otherwise-lenient preponderance evidentiary standard. This is not a close case. Petitioners have not established entitlement to a damages award.[39]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[39] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.