In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS
No. 02-1314V
(To be Published)

BRUCE ANDERSON and DONNA ANDERSON, as parents and natural guardians of R.A., a minor,	*	Special Master Corcoran
	*	Filed: November 1, 2016
Petitioners, v.	*	Entitlement Decision; Measles, Mumps, and Rubella ("MMR"); Autism Spectrum Disorder ("ASD"); Mitochondrial Disease
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Ronald Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for petitioners.

Jason Bougere, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On October 1, 2002, Bruce and Donna Anderson filed a petition on behalf of their child, R.A., seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program").[2] The Andersons sought to establish that the measles, mumps, and rubella ("MMR") vaccine that R.A. received on December 13, 1999, exacerbated an underlying mitochondrial disorder, in turn causing him to experience a

[1] Because this decision contains a reasoned explanation for my action in this case, it will be posted 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 Vaccine Rule 18(b), each party has 14 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 entire decision will be available to the public.

[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.

developmental regression ultimately manifesting as an Autism Spectrum Disorder ("ASD").

A hearing was held on December 8-9, 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

The record in this case consists of the following: R.A.'s medical records; an affidavit from R.A.'s father (co-petitioner Bruce Anderson), as well as his live testimony; the written reports and testimony of two experts (one for each side); and medical or scientific literature submitted by the parties in support of their respective positions. I have reviewed the entire record as required by the Vaccine Act. Section 13(a)(1).[3]

A. R.A.'s Early Medical History

R.A. was born on December 10, 1998, following a normal pregnancy and delivery by caesarean section, and shortly thereafter was assessed as a well-child at an early pediatric visit approximately two weeks later. Pet'rs' Ex. 2 at 10, 15; Ex. 5 at 77. In the following months, R.A.'s pediatrician, Laura Beverly, M.D., at Children's Medical Group, P.A., was consulted regarding various parental concerns, including bacterial and viral infections. *See, e.g.*, Pet'rs' Ex. 5 at 73-74 (R.A. seen for yeast infection); *id.* at 72 (seen for cold symptoms and a rash); *id.* at 67-68 (mother reported R.A. vomiting with fever). In the first year of his life, R.A. received several routine childhood immunizations, in accordance with the vaccination schedule set forth by his doctor.[4]

[3] The medical records in this case are voluminous, and include many records pertaining to R.A.'s post-vaccination treatment that bear only tangentially on the issues to be resolved in this entitlement proceeding, since they do not relate to the causal effect of the relevant vaccines. Accordingly, I do not discuss all such medical records in detail, but instead focus on what both sides have identified as the most significant records relevant to the causation issues presented herein. *See Paterek v. Sec'y of Health & Human Servs.,* 527 Fed. App'x 875, 884 (Fed. Cir. 2013). The same goes for the extensive medical literature submitted by both sides; I have reviewed all such literature filed in preparing my decision, even if each individual piece of literature is not specifically discussed in this decision. *Moriarty v. Sec'y of Health & Human Servs.*, No. 15-5072V, 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). A meaningful discussion of all of the literature offered in this case would double or triple the size of this decision, without providing any further illumination as to the reasoning behind it.

[4] Thus, on January 13, 1999, R.A. received his first Hepatitis B ("Hep. B") vaccination. Pet'rs' Ex. 5 at 7. On February 15, 1999, R.A. received several additional vaccines, including: a second Hep. B vaccination; the

On February 15, 1999, R.A. had a two-month well-child visit where he was reported to smile, lift his head, and was noted as being active, alert, and healthy. Pet'rs' Ex. 5 at 73-74. R.A. again saw his pediatrician in March 1999 after his mother reported thrush, cold symptoms for nine days, and a rash on his face. *Id.* at 72-74. R.A. was diagnosed with a viral infection. *Id.* at 72. By his next well-child visit on April 5, 1999, however, he was reported as healthy. *Id.* at 71.

R.A. next saw his pediatrician for his six-month well-child visit on June 2, 1999, where he was reported as playful and healthy. Pet'rs' Ex. 5 at 70. Two months later, in August 1999, R.A. was reported as having a fever and vomiting, but no diarrhea. *Id.* at 67. R.A. was taken to the hospital for gastroenteritis on August 11, 1999. *Id.* at 68. However, at his next well-child visit on September 9, 1999, R.A. was again characterized as healthy and active. *Id.* at 67.

B. December 13, 1999 Vaccination and Purported Reaction

R.A. returned to the pediatrician for his one-year well-child visit on December 13, 1999. Pet'rs' Ex. 5 at 66; Tr. at 12. At this time, R.A. received his first MMR and Varicella vaccinations. Pet'rs' Ex. 5 at 7. Records from the visit indicated that R.A. continued to be characterized as healthy and normal in development. *Id.* at 66. Six days later, on December 19, 1999, R.A.'s mother telephoned the pediatrician reporting that R.A. had been running a high fever (103.3 degrees on the prior day) and was slightly congested, but otherwise generally happy. *Id.* at 63. R.A. was therefore brought back to his pediatrician the next day, December 20, 1999, and the Andersons reported that R.A. had been suffering from a runny nose for several days, followed by a high fever for only the past day. R.A.'s temperature at that time was 101.6 degrees, but the examination notes state that R.A. was otherwise alert and awake with clear rhinorrhea and nasal congestion. *Id.* R.A. was diagnosed with "viral syndrome/viral URI [upper respiratory infection.]." *Id.* There is no mention made of a relationship between R.A.'s viral episode and a vaccine as of this pediatric visit.

That evening (the seventh day after R.A. received the MMR vaccine), R.A.'s fever spiked to over 105 degrees, according to Mr. Anderson's trial testimony. Tr. at 13. After

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combination vaccine DTP-Hib, which includes vaccinations for diphtheria, tetanus, pertussis ("DTP"), and Haemophilus influenza type b ("Hib"); and an oral polio vaccine. *Id.* Then, on April 5, 1999 R.A. received a second DTP-Hib vaccine and a second oral polio vaccine. *Id.* On June 2, 1999, R.A. received three more vaccinations: a third DTP vaccine, a third Hib vaccine, and a third oral polio vaccine. *Id.* On September 9, 1999, R.A. received his third Hep. B vaccination. The record sets forth no particular instance after any of these vaccinations when R.A. experienced a notable reaction.

contacting the pediatrician again, the Andersons were instructed to take R.A. to the emergency room, and they did so. *Id.* at 13-15. R.A.'s temperature at that time was officially recorded to be 105.1 degrees, and the emergency treaters took blood cultures and started him on an antibiotic, but he was not admitted overnight and went home. Pet'rs' Ex. 19 at 2, 5-6; Tr. at 13. The Andersons brought R.A. back to the pediatrician the next day, on December 21, 1999, and although he was still running a fairly high fever (102.2 degrees), he was nevertheless described as awake and alert with clear rhinorrhea. Pet'rs' Ex. 5 at 64. The pediatrician opined that R.A.'s illness was "probably viral," but recommended continuing antibiotics pending the result of the blood cultures. *Id.*

R.A.'s fever thereafter persisted for roughly two days, abating around December 22, 1999. Tr. at 15. That day, in a telephone call with the pediatrician, R.A.'s mother reported that he had slept all afternoon, was eating and drinking well, and doing "much better." Pet'rs' Ex. 5 at 63.

C. R.A.'s Health History in Early 2000

The contemporaneous records do not document any subsequent progressive worsening of R.A.'s overall health in the six months immediately following his December 1999 vaccinations, nor do they set forth treater concerns about any related symptoms. However, R.A. was taken back to the pediatrician several times in the ensuing period, and it is the Petitioners' allegation that these subsequent visits were precipitated by a reaction to the MMR vaccination.

Thus, in January 2000, R.A. was seen by his pediatrician three times. First, on January 20, 2000, R.A. was reported to have had a cold for two days with pink, swollen eyes, and was diagnosed with conjunctivitis. Pet'rs' Ex. 5 at 62. Next, on January 28, 2000, R.A. was diagnosed with exudative tonsillitis after presenting with a fever, and being reported as clinging, fussy, with a decreased appetite and bright red and white tonsils. *Id.* at 61. Later, on January 30, 2000, R.A. was taken back to the pediatrician due to discovery of a red area at the base of his penis, and was diagnosed with a probable penile adhesion due to pulling. *Id.* at 60. None of the records from these visits, however, link any of the diagnosed conditions or illnesses with the MMR vaccine, and the records filed do not link them as part of a progressive set of related symptoms.

There are no medical records reporting any illnesses for R.A. in February 2000. On March 3, 2000, R.A. was taken to the pediatrician with a fever and a sore throat, and diagnosed with pharyngitis and viral-like rash. Pet'rs' Ex. 5 at 59. Later that same month, on March 22, 2000, R.A. again saw the pediatrician for his fifteen-month well-child visit.

Id. at 58. At this time, however, R.A. was reported as being healthy, developing and walking well for the past two months, and saying about five words. *Id.* at 58.

Six weeks later, in May 2000, R.A. went to his pediatrician following a visit to the emergency room due to a fever and lethargy. Pet'rs' Ex. 5 at 57. At the follow-up visit on May 30, 2000, R.A. was still running a fever, and was reported to be suffering from diarrhea for two days. *Id.* R.A. was taken to the pediatrician on two more occasions that same month, either because of recurring diarrhea or pharyngitis. *Id.* at 55-56; Pet'rs' Ex. 41 at 1.[5]

D. Concerns about R.A.'s Development

The first medical records hinting at possible developmental concerns for R.A. are not found until June 2000. At that time, R.A. was taken to the pediatrician for an 18-month well-child checkup. Pet'rs' Ex. 5 at 53-54. In addition to consideration of R.A.'s diarrhea from the prior month (*Id.* at 55; Pet'rs' Ex. 41 at 3), the records from this checkup mention R.A.'s developmental status. Thus, R.A.'s pediatrician observed his word usage, noting that R.A. was able to say "hi," "bye," and "dada." *Id.* R.A. would also come when called, would look up if asked "where is the moon," would say "moo" if asked what a cow said, and had a "good response to no." *Id.* Overall, R.A. was deemed a healthy eighteen month-old, normal in development. *Id.* at 53. However, two concerns are noted in these records as well, without characterizing their significance: R.A. did not "really follow commands," and he would not point out pictures in books. *Id.*; Pet'rs' Ex. 41 at 4. Accordingly, although the records from this pediatric visit are the first in which any concerns about R.A.'s development are noted, they are inconclusive in their characterization of that development.

There is thereafter a multi-month gap in the medical history, with no evidence of any subsequent doctor's visits until September 11, 2000, when R.A. underwent his 21-month well-child visit. The records from that visit described R.A. as a healthy 21-month old that could sing the vowels, understood "no" and slept well. However, R.A.'s doctor reiterated prior concerns about R.A.'s following of commands and interactivity first noted in June, and stated she had "some developmental concerns." Pet'rs' Ex. 5 at 52-53. R.A.'s pediatrician therefore recommended a speech and hearing evaluation. *Id.* at 51. By his two-year well-child visit on December 6, 2000, R.A.'s developmental delays had become more pronounced and self-evident. *Id.* at 50. Thus, R.A.'s pediatrician reported that R.A.

[5] The pediatric records are primarily handwritten and some portions of difficult to read. Petitioners provided transcribed portions of the pediatric record as Pet'rs' Ex. 41, but the transcriptions did not include R.A.'s visit of May 30, 2000.

did not have 20 words despite progress in other areas. *Id.* at 50. He was recommended for further evaluation, including genetics testing. *Id.* However, his health was otherwise deemed good, and throughout the entirety of 2000, R.A. continued to receive scheduled vaccinations. *Id.* at 7.

E. Efforts to Treat R.A.'s Developmental Problems

Once R.A.'s developmental problems were clearly evident, the Andersons began a comprehensive effort to discern their cause and treat them effectively, seeking input from a variety of medical specialists including pediatric, neurocognitive, dietary, and genetic specialists. In the course of their efforts, R.A. underwent numerous behavioral, genetic, and biological evaluations.[6]

On January 11, 2001, R.A. was evaluated by Laura Bailet, Ph.D., a neurocognitive specialist at the Nemours Children's Clinic in Jacksonville, Florida. Pet'rs' Ex. 3 at 5-7. During the initial evaluation, R.A.'s parents provided a history of R.A.'s development, informing Dr. Bailet that R.A. was generally very healthy, with no significant illnesses, accidents, or hospitalizations to date. *Id.* at 5. They also reported that R.A.'s motor coordination was fair, but characterized his language skills as poor. Specifically, the Petitioners reported that he had spoken his first words prior to turning one, but since that time showed very slow language progression. They also noted that, while R.A. could say a few understandable words, he primarily babbled, pointed, or reached for what he wanted. *Id.* at 6. Based upon the recited history, Dr. Bailet recorded that "no history of frank language regression was reported." *Id.* After a second evaluation on January 25, 2001, Dr. Bailet concluded R.A. showed developmental delays and several mild behavioral characteristics that could be associated with autism. *Id.* at 30.

R.A. was next evaluated by Daniel Shanks, M.D., a pediatric neurologist, on January 31, 2001. Pet'rs' Ex. 3 at 17. Dr. Shanks's notes record the Andersons informing him that they had harbored "concerns all along in regard to [R.A.'s] language development," but otherwise recounted "no evidence of developmental regression," as opposed to a more general failure to progress developmentally. *Id.* Dr. Shanks also reported that "[w]ith motor development, [R.A.] has had no significant difficulty other than being a little bit clumsy but is very loose-jointed." *Id.* Dr. Shanks diagnosed R.A. with static encephalopathy with a communication disorder spectrum, and stated it would be

[6] In addition to seeking advice from medical professionals, the Andersons also initiated their own research into possible causes of R.A.'s developmental delays starting around the winter of 2001. Tr. at 37-38. This included researching alternative diets such as those set forth in the cookbook *Special Diets for Special Kids* by Karyn Seroussi and Lisa Lewis. Tr. at 37-38. The Andersons also conducted their own review of medical literature on pervasive developmental disorder and autistic spectrum disorder. Tr. at 41; Pet'rs' Ex. 3 at 38.

reasonable to consider genetic testing. *Id.* at 19. Dr. Shanks also noted that R.A.'s "very limber" joints may have been inherited from his mother's side of the family, while his "low tone and ligamentous laxity" could be unrelated. *Id.* at 18.

R.A. received a genetic evaluation from Pamela Arn, M.D., on February 5, 2001. Pet'rs' Ex. 3 at 22-24. The genetic testing revealed normal chromosomes. *Id.* at 38-39. However, the records from this evaluation elaborate on the nature and timing of R.A.'s developmental problems. Dr. Arn's history noted that R.A.'s mother first became concerned about R.A.'s development when he was 15 months old (or in March 2000 – months before the first record evidence of developmental concerns), at which time she began to observe delays in his verbal and interactive skills. *Id.* at 22. Dr. Arn also stated that R.A. showed no other problems with other physical systems. *Id.* at 23. R.A. was reported as being a picky eater, but would generally eat foods from all food groups without difficulty, and he had no current food intolerance. *Id.* He had not had any seizures or any neurologic episodes suspicious for seizures. *Id.* R.A.'s motor milestones were overall deemed normal, with only his verbal skills characterized as delayed. *Id.*

R.A. was then evaluated two months later, on April 12, 2001, by Donald George, M.D., a gastroenterologist at Nemours Children's Clinic. Pet'rs' Ex. 3 at 41-43. The Andersons contacted Dr. George for information and advice relating to dietary control of behavior. *Id.* at 41. Dr. George's report of the visit notes that the Andersons first became concerned about R.A.'s developmental progress in the fall of 2000 (when R.A. would have been 20-21 months old). *Id.* at 41. After conducting their own research, the Andersons had become interested in the possibility that R.A.'s behavior reflected autistic tendencies, and began to pursue diet restrictions and other treatments recommended by some of the independent specialists they had contacted. *Id.* at 41. Thus, Dr. George reported, R.A. had been taking a wide variety of supplements, including dimethyl glycine, glutamine, acidophilus, fluoride, diflucan, and a variety of proprietary vitamins. *Id.* at 42.

R.A. was next evaluated by Dr. Karoly Horvath, M.D., a pediatric gastroenterologist, on June 7, 2001. Pet'rs' Ex. 6. Dr. Horvath performed endoscopies, biopsies, and microbiologic analysis of body fluid cultures. *Id.* at 23-35. Dr. Horvath found no significant abnormalities or pathology from these evaluative tests, however. *Id.* R.A. was later seen again by Dr. Bailet on November 12, 2001, when R.A. was 25 months old. Pet'rs' Ex. 3 at 61-65. Dr. Bailet concluded that R.A. was currently functioning at an 18-month level overall in language skills, and scored as moderate-to-severely autistic on the autism rating scale. *Id.* at 64.

Beginning in 2001, R.A. started receiving treatment from Dan Rossignol, M.D. and Jeffrey Bradstreet, M.D.,[7] two doctors associated with the "Defeat Autism Now" ("DAN!") project.[8] Among the treatments prescribed to R.A. by Drs. Rossignol and Bradstreet were intravenous infusions of Intravenous Immunoglobulin ("IVIG"), Vitamin C, Secretin, Solumedrol, and glutathione. Pet'rs' Ex. 13 at 353. In a justification of these treatments from a record dated February 6, 2008, Dr. Bradstreet stated that "[R.A.] suffered neurological, gastrointestinal, and immune system injuries and dysfunction as a result of vaccines, including but not limited to persistent measles virus infection, post measles encephalitis, chronic diarrhea, and inflammatory bowel disease (IBD) from his Measles Mumps Rubella (MMR) vaccination at 12 months of age." *Id.* at 876. Notably, this is the first medical record in which any treater not only connects R.A.'s autism diagnosis to the MMR vaccine, but places the onset of his developmental symptoms at the time of vaccination.

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[7] Dr. Bradstreet was a practicing physician who specialized in children with autism spectrum disorder and attention deficit hyperactivity disorder, and who espoused the belief that there is a causal link between autism and the MMR vaccine (particularly due to what he alleged to be toxic amounts of mercury contained within the vaccine). *See, e.g.*, *Hearing before the Committee on Government Reform*, June 19, 2002, Serial No. 107-121, available at https://www.gpo.gov/fdsys/pkg/CHRG-107hhrg82358/html/CHRG-107hhrg82358.htm (site last visited on October 31, 2016). But treatments promoted by Dr. Bradstreet have not been proven effective, and even termed dangerous. Trine Tsouderos and Patricia Callahan, *Risky alternative therapies for autism have little basis in science*, Chicago Tribune, Nov. 22, 2009 (treatments such as chelation therapy and hyperbaric chamber therapy sessions are unproven and potentially dangerous). Dr. Bradstreet committed suicide on June 19, 2015, shortly after his clinic was raided by state and federal authorities. Michael E. Miller, *Anti-Vaccine Doctor behind 'Dangerous' Autism Therapy Found Dead. Family cries foul*, Washington Post, June 29, 2015, available at https://www.washingtonpost.com/news/morning-mix/wp/2015/06/29/anti-vaccine-doctor-behind-dangerous-autism-therapy-found-dead-family-cries-foul/ (site last visited October 31, 2016).

[8] 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 October 31, 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.*

ARI discontinued the DAN! Protocol in 2011, however, 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 Oct. 31, 2016).

R.A. was also evaluated for possible seizure disorder in May 2002 following a reported history of 15 seconds of eyes rolling up and absence. Pet'rs' Ex. 13 at 702. An EEG was recorded, which indicated multiple episodes of 3-cycle spikes and waves lasting less than 1.5 seconds. R.A. was subsequently diagnosed with absence seizures.[9] *Id.*

In 2003, R.A. began receiving care at Progressive Pediatrics, where he received intramuscular immunoglobulin ("IMIG") regularly from October 2003 until January 2005. Pet'rs' Ex. 4 at 4-35. R.A. also received treatments in a hyperbaric chamber three times each week during the summer of 2005.[10] *Id.* at 38. R.A. continued to receive care at Progressive Pediatrics for both sick visits and well-child visits until at least 2010. *Id.* at 68. During that time, a diagnosis of "active autism" was consistently noted.[11]

F. Consideration of Mitochondrial Disorder as Basis for R.A.'s Condition

Starting in 2001, R.A. was periodically tested for various markers of metabolic abnormalities, including ammonia, lactic acid, and liver enzymes aspartate transaminase ("AST") and alanine transaminase ("ALT"). *See* Pet'rs' Ex. 13 at 22-268. Dr. Bradstreet deemed some results as significant, including evidence of a low free and total carnitine[12],

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[9] Absence seizures or absence epilepsy is characterized by staring spells that can last 1-10 seconds. http://www.mayoclinic.org/diseases-conditions/petit-mal-seizure/basics/definition/con-20021252 (last visited Oct. 31, 2016). Absence seizures generally do not elicit the same behavior as grand mal seizures where the subject falls to the ground, but instead was described by Dr. Cohen, respondent's expert, as if "[t]heir circuit-breakers have been resent." Tr. at 222.

[10] Hyperbaric oxygen therapy (which is used to treat a variety of conditions) involves breathing pure oxygen in a pressurized room or body-sized tube. *Tests and Procedures: Hyperbaric Oxygen Therapy*, Mayo Clinic (Nov. 25, 2014), http://www.mayoclinic.org/tests-procedures/hyperbaric-oxygen-therapy/basics/risks/prc-20019167?B p=1 (last visited Oct. 31, 2016). When an individual is placed in a hyperbaric oxygen therapy chamber, air pressure is increased to three times higher than normal, permitting the lungs to gather more oxygen than would be possible at normal air pressure. *Id.* The individual's blood then carries this oxygen throughout the body, which purportedly helps fight infection and promotes healing. *Id.* However, medical science has not confirmed that hyperbaric oxygen therapy is an effective autism treatment. *Id.* Moreover, although hyperbaric oxygen therapy is generally a safe procedure, it does involve risks, including the possibility of lung collapse, middle ear injuries, and seizures. *Id.*

[11] Throughout this period, R.A. was receiving a significant number of medications and supplements. As of July 21, 2008, they included Gamunex immunoglobulin (IVIG), SecreFlo Secretin, Gluthathione and Cysteine, Zyrtec, Spironolactone, Methyl-B12, Digest Right 1, Nordic Natural Cod Liver Oil, Probiotic Pearls, Ther-Biotic Complete, Nordic Natural ProEPA, Calcium and magnesium tablets, Child Essence multi-vitamin, FolaPro, L-Carnitine, Coenzyme Q10, Ester-C, Taurine, Zinc, NasalCrom, and Ayr Saline. Pet'rs' Ex. 13 at 461-62.

[12] Carnitine is a substance necessary for the digestion of fatty acids. Testing for "free" carnitine tests how much usable carnitine a subject has and compares it with the total amount in the subject's body.

increased lactate[13] and increased ammonia[14]. Pet'rs' Ex. 13 at 460. However, test results suggesting the existence of abnormal biochemical markers were inconsistent with other tests indicating that R.A.'s free and total carnitine, lactate, and ammonia were not, in fact, elevated. *See* Pet'rs' Ex. 13 at 961 (indicating normal free and total carnitine on February 5, 2001), Ex. 13 at 24, 53, 60, 83 (showing normal levels of lactic acid on July 23, 2008; January 23, 2009; June 1, 2009; and October 1, 2010), and Ex. 13 at 24, 51, 59, 130, 143, 146, 156, 171, 185 (showing normal ammonia on January 20, 2005; August 17, 2005; April 12, 2006; April 28, 2006; June 14, 2006; February 2, 2007; January 23, 2009; July 27, 2009; and October 1, 2010).

In 2008 – significantly, more than seven years after R.A. had received the MMR vaccine – R.A. was referred to John Shoffner, M.D., a specialist in mitochondrial disorders, for an evaluation to determine whether R.A.'s developmental limitations were attributable to a defect in cellular energetics or another class of metabolic disease. Pet'rs' Ex. 10 at 15. Dr. Shoffner evaluated R.A. on July 22, 2008 at Medical Neurogenetics in Atlanta, GA, and conducted a series of tests including muscle biopsies and metabolic studies, in additional to reviewing R.A.'s medical history. Pet'rs' Ex. 10 at 15; Pet'rs' Ex. 9 at 42. The muscle biopsies were performed at the Pediatric Center at Atlanta Outpatient Surgery Center (*see* Pet'rs' Ex. 10 at 26), while the metabolic studies involved samples taken from R.A. on July 23, 2008 and then analyzed at Medical Neurogenetics, LLC, also in Atlanta, Georgia. *See* Pet'rs' Ex. 9 at 1.

After reviewing the lab results, Dr. Shoffner diagnosed R.A. with a mitochondrial disease and renal tube dysfunction. Pet'rs' Ex. 9 at 42. But his diagnosis relied heavily on what had been recounted to Dr. Shoffner about the timing of R.A.'s developmental difficulties. Thus, Dr. Shoffner reported (without corroboration from the medical record) that R.A. had been developing normally until his MMR vaccination at 12 months of age. Pet'rs' Ex. 9 at 42; Ex. 10 at 15. Following that, he continued, R.A. developed a high fever,

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https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=carnitine_total_free (last visited October 31, 2016). R.A. exhibited low levels of free and total carnitine in samples taken on April 29, 2008. Pet'rs' Ex. 13 at 112.

[13] Increased lactate was shown in samples taken on April 29, 2008 and June 27, 2008. Pet'rs' Ex. 13 at 100, 101.

[14] Increased ammonia was reflected in several samples, including those taken on December 10, 2001; January 20, 2005; April 27 2007; April 29, 2008; June 27, 2008; December 22, 2008; and June 1, 2009. Pet'rs' Ex. 13 at 52, 64, 99, 111, 126, 184, and 268. Ammonia levels can be significant because they can act as indirect biochemical markers of mitochondrial dysfunction. See, e.g., D. Rossignol et al., *Mitochondrial Dysfunction in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis*, Mol. Psych. 17, 290-314 at 292 (2012). Further, according to Petitioners' expert Dr. Huq, higher levels of ammonia over a long period of time can also damage the brain. Tr. at 117-18.

although he acknowledged that it was not associated with any immediately evident neurological changes. Pet'rs' Ex. 10 at 15. He then recounted that R.A. had received another vaccine at 16-17 months of age associated with a fever, and that shortly thereafter, at 17-18 months of age, experienced a regression of skills including a loss of speech, motor skills, cognitive ability, and receptive/expressive speech. Pet'rs' Ex. 10 at 15, Ex. 9 at 42. As already noted, however, no evidence of a second fever, or a skills/language regression, is found in the medical records already discussed (although there is evidence of a number of URI-related fevers from the winter and early spring of 2000).

Besides R.A.'s recounted medical history, Dr. Shoffner's diagnosis relied on extensive evaluations of various metabolic marker test results, including free and total carnitine levels, lactose levels, and the concentration of amino acids in R.A.'s cerebral spinal fluid, blood plasma, and urine. Pet'rs' Ex. 9 at 4, 5, 25, 31. Dr. Shoffner's testing indicated that carnitine levels were normal. Pet'rs' Ex. 9 at 1. R.A.'s lactate levels as measured in his cerebral spinal fluid ("CSF") were also within normal ranges, but slightly elevated in his plasma. *Id.* at 5, 26; Tr. at 133-34. R.A.'s amino acid levels showed a normal profile as measured in his CSF and plasma (Pet'rs' Ex. 9 at 4, 5, 25, 42), but R.A.'s urine showed elevations of multiple amino acids, including taurine, glutamine and cysteine. Ex. 9 at 31. Based on the increased urine amino acids, Dr. Shoffner concluded that R.A. had a proximal renal tubule defect causing a generalized aminoaciduria[15]. Pet'rs' Ex. 9 at 31, 41-42. Dr. Shoffner specifically discounted the possibility that the elevated levels of amino acids were related to supplements he was taking at the time. *Id.* at 42.[16]

Dr. Shoffner also conducted a biopsy of R.A.'s skeletal muscles in order to perform enzymology tests. In particular, Dr. Shoffner conducted a variety of assays to determine the activity of various mitochondrial enzymes, referred to as Complexes I through IV, by testing the functioning of mitochondria found in biopsied muscle tissue samples. Pet'rs' Ex. 9 at 24; *see also Id.* at 49 (additional background information regarding mitochondrial

[15] Aminoaciduria is an excess of amino acids in the urine. This can be caused by a general excessive level of a given amino acid in the blood or defective transport mechanisms for amino acids in the renal tubules of the kidneys. *Dorland's Illustrated Medical Dictionary* 61 (32nd ed. 2012) (hereinafter "*Dorland's*").

[16] Dr. Cohen testified during the hearing of this matter that R.A.'s elevated amino acids could be attributable to the supplements he was prescribed - and specifically supplements purportedly not reflected in Dr. Shoffner's report, such as taurine or 3-methyl glycine. In fact, however, Dr. Shoffner's report recognized that R.A. had been prescribed 975 mg of taurine. *See* Pet'rs' Ex. 10 at 17.

function)[17]. Only one of the two assays conducted evaluating Complex I activity, however, suggested reduced enzyme activity. *Id.* Rather, the Complex I assay results overall fell within the normal range to a 95 percent confidence interval. Pet'rs' Ex. 9 at 24. Of the two assays evaluating Complex IV, only one indicated reduced activity. *Id.* The study also showed a reduction in citrate synthase - an important marker enzyme in the mitochondria that provides a proxy measurement of mitochondrial content in the muscle.[18]

Dr. Shoffner examined R.A.'s muscle fibers, conducting a physical examination of them under a microscope, a histochemistry analysis, and an immunochemistry analysis. Pet'rs' Ex. 9 at 9, 41. Dr. Shoffner observed a moderate size variation due to atrophy of one type of muscle fiber, Type II, and increased myofiber lipids. *Id.* at 9. The histochemical and immunochemical analyses were unremarkable, however. *Id.* at 9, 41.

Following the evaluation of R.A.'s laboratory tests and muscle biopsies, Dr. Shoffner diagnosed R.A. with a "probable oxidative phosphorylation disease," Complex I defect, and ASD with proximal renal tubule defect. Pet'rs' Ex. 9 at 42. Based on the recommendations of Drs. Bradstreet and Shoffner, R.A.'s supplements were changed to include substances more targeted to affect mitochondrial function, such as carnitine and ribose. Tr. at 64-65; Pet'rs' Ex. 13 at 443.

Dr. Frances Kendall, a clinical biochemical geneticist, also evaluated R.A. and performed genetic testing on December 30, 2013. Pet'rs' Ex. 26 at 12. The history section from the records of this evaluation noted that R.A.'s early development was normal, but that Petitioners had observed R.A. begin to withdraw socially and lose skills immediately following his receipt of the MMR vaccine and febrile illness (contrary to the medical records discussed above, which do not document even incipient concerns about R.A.'s speech until he was 19 months old). Pet'rs' Ex. 26 at 1. Dr. Kendall determined that there were two mutations present in R.A. which have been linked to intellectual disability, neurodevelopmental disorders, and autism. *Id.* at 10. However, Dr. Kendall acknowledged that these variants were of uncertain significance, stating "it is purely speculative as to whether or not they are causative for [R.A.]". Pet'rs' Ex. 26 at 10.

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[17] Complex I is a term describing a group of proteins in the mitochondria that are integral to the production of cellular energy. Typically, five protein complexes (referred to as Complex I – V) work in sequence in the mitochondria to produce cellular energy. *See* Pet'rs' Ex. 9 at 48-49.

[18] Citrate synthase is an enzyme in mitochondria. Salvatore DiMauro and Eric Schon, *Mitochondrial Respiratory-Chain Diseases,* N. England J. Med., 348 (26) at 2657 (2003); *Dorland's* at 455. It is used as a marker enzyme to increase the diagnostic reliability of mitochondrial testing. *See* Bruce Cohen, *Neuromuscular and Systemic Presentations in Adults: Diagnoses Beyond MERRF and MELAS*, Neurotherapeutics (10) 227-42 at 239.

After the evaluation by Dr. Shoffner, R.A. experienced improvements in his energy to the point where he could maintain significant physical activity for 3-6 hours a day. Tr. at 66-67. Today, R.A. has made advances in his physical and mental development. R.A. is participating in basketball and enrolled in a high school for high-functioning children. However, R.A. still goes to speech therapy, and his level of abstract thinking is not as advanced as others his own age. Tr. at 72-74.

II. TESTIMONY PRESENTED AT HEARING

A. Mr. Anderson

Mr. Anderson provided fact testimony regarding the circumstances of R.A.'s alleged vaccine reaction and subsequent condition, along with information about R.A.'s treatment over the past several years.

Prior to R.A.'s 12-month well-child visit on December 13, 1999 at which he received the MMR vaccine, R.A. appeared to Mr. Anderson to be developing normally - pointing and gesturing at objects, making eye contact, and vocalizing basic words like "mama" or "dada." Tr. at 10-12. Mr. Anderson testified, however, that within a few days of receiving the MMR vaccination, R.A. became lethargic and had a low-grade fever, eventually spiking (in several days) to over 105 degrees. *Id.* at 13. After contacting R.A.'s pediatrician's office, the Andersons took R.A. to the emergency room. *Id.* at 13-15. R.A.'s fever persisted for roughly two days, and, according to Mr. Anderson, abated around December 22, 1999. *Id.* at 15.

Immediately following R.A.'s fever and emergency room visit, Mr. Anderson observed R.A. to be "low-energy," "fussy and tired," and not interested in the toys he received for Christmas. Tr. at 18-19. Mr. Anderson also stated that R.A. was not interacting well with family members. Specifically, R.A. was not as engaging in terms of eye contact, did not want to be hugged or held, and "there was not the quantity and quality of smiles and laughs that we saw before." Tr. at 19.

Between January and June of 2000, Mr. Anderson recalled a gradual but progressively worse change in R.A.'s behavior and development.[19] Tr. at 23-26. R.A. began to avoid eye contact, did not want to be held, and lost interest in books and gesturing for things he desired. *Id.* at 24. Mr. Anderson also testified that R.A.'s babbling

[19] Mr. Anderson specifically testified that he noticed a change in R.A.'s behavior starting around January 2000, but also admitted that his schedule was extremely busy, and therefore his opportunities to observe closely changes in R.A. were more limited throughout the early part of that year. Tr. at 9-10.

gradually started "sounding less like he was trying to speak and becoming more, like, tantrums or meltdowns or just screaming." *Id.* R.A.'s diet became significantly more limited in this period, a change coinciding with the development of chronic diarrhea starting around the end of May 2000 and lasting for several years. *Id.* at 29-31.

Although Mr. Anderson sought to place the onset of R.A.'s developmental problems in the days and weeks after receipt of the MMR vaccine in December 1999, he admitted that neither he nor his wife ever raised any concerns with R.A.'s pediatrician in this time period (consistent with the actual records as discussed above). Tr. at 27-28. Mr. Anderson attempted to explain this omission by asserting that he and his wife felt that R.A. would just get better as soon as they could devote more time to him, and therefore did not see the need to raise the issue with an existing treater. *Id.* at 28.

At the same time that R.A. was purportedly observed displaying early developmental problems, Mr. Anderson testified, he was also seen to be in declining health in other respects. Thus, Mr. Anderson stated that he and his wife had to take R.A. to the pediatrician regularly for treatment of various ailments, including low-grade fever, runny nose, and congestion, compared to the time before R.A. received the MMR vaccination. Tr. at 27.

Following R.A.'s diagnoses of autism, the Andersons began educating themselves on the disorder by conducting research on the internet, reading books, and attending educational conferences aimed at parents of autistic children. The first time Mr. Anderson was introduced to the concept that the MMR vaccine may have contributed to R.A.'s autism was based on his own research, either upon reading a book by Karyn Seroussi in early 2001, or after attending a DAN! Conference in April of 2001. Tr. at 84-86. After the DAN! Conference, Mr. Anderson had several exchanges with R.A.'s pediatrician, in which he disputed her assertions about the comparative safety of vaccines. *Id.* at 87.

By the end of 2000, the Andersons had begun a comprehensive treatment program for R.A., including speech and occupational therapy. Tr. at 36. The Andersons also pursued various therapies on their own based on their personal autism treatment research (and concordant views about it). For example, the Andersons decided to remove gluten and casein from R.A.'s diet in early 2001. *Id.* at 37-39. They also began administering various medications and supplements, such as cod liver oil, probiotics, and colostrum for his diarrhea. *Id.* at 45.

Mr. Anderson asserted his overall belief that the care and treatment R.A. had received had resulted in slow and gradual improvement in his development and overall

health. Tr. at 38-41, 46-47. Mr. Anderson also asserted that R.A.'s therapists and pediatrician had themselves observed these improvements. *Id.* at 38-40, 46-47, 66-68.

B. Petitioners' Expert - Dr. Ahm Mahbubul Huq

Ahm Mahbubul Huq, MBBS, Ph.D., offered two expert reports plus testimony at the entitlement hearing in support of Petitioners' claim. *See generally* Pet'rs' Ex. 27, Medical Expert Report of Ahm Mahbubul Huq, MBBS, Ph.D., dated September 21, 2014 (the "Huq Rpt."); Pet'rs' Ex. 29, Supplemental Medical Expert Report of Ahm Mahbubul Huq, MBBS, Ph.D., dated May 11, 2015 (the "Huq Supp. Rpt."); Tr. at 90-205. Overall, Dr. Huq theorized that R.A.'s MMR vaccination led to a febrile illness and significantly aggravated R.A.'s alleged underlying mitochondrial dysfunction (which predisposed R.A. to further deficits in cellular energy metabolism), resulting in an encephalopathy with features of autism spectrum disorder. Huq Rpt.at 6.[20]

Dr. Huq is a board-certified neurologist with a special qualification in child neurology and clinical genetics. Tr. at 92, Pet'rs' Ex. 28. Dr. Huq graduated from Dhaka Medical College in Bangladesh, and went on to study in Japan, focusing on a number of areas including pyruvate metabolism disorder, pyruvate dehydrogenase deficiency, stem cell transplantation, and dopamine metabolism. Tr. at 91, Pet'rs' Ex. 28. Following that, Dr. Huq completed a residency in neurology and genetics, and several years in clinical and medical genetics. *Id.* After training in genetics, Dr. Huq completed a child neurology program, and is currently a professor of pediatrics and neurology at Wayne State University. He has also conducted research as a faculty member, mostly in the area of autism and the genetics of autism. Tr. at 92. In addition, Dr. Huq has published roughly 40 articles on the topics of "inborn errors of metabolism, pyruvate dehydrogenase deficiency and mostly clinical work in vitamin D receptor metabolism," as well as hematopoietic stem cell transplantation, autism, and other clinical observations. *Id.* at 93.

Dr. Huq's opinion centered on the question of whether R.A. suffers from an underlying mitochondrial disorder[21] – a question he answered in the affirmative. He began

[20] As discussed in greater detail below, although Dr. Huq's reports initially characterized R.A.'s developmental problems as manifesting as a regression in previously acquired skills, he clarified at hearing that in fact the medical record evidence did not support the conclusion that R.A. ever regressed at all. Tr. at 177-85. He therefore backed away from his prior embrace of the term "regression," characterizing R.A.'s reaction as a failure of development. *Id.* at 185-86.

[21] Notably, and by Dr. Huq's admission, the vast majority of Dr. Huq's patients (based on those seen on a yearly basis) do not have mitochondrial disorders (Tr. at 190) – thus reducing somewhat his expertise in diagnosing the condition (although he also has experience with metabolic disorders more generally).

by explaining his understanding of mitochondrial diseases and disorders generally. Monogenic mitochondrial disease, he proposed, is caused by a recognized single gene mutation, resulting in a defined diagnosis such as Leigh Disease.[22] Tr. at 103. By contrast, mitochondrial *dysfunction* occurs when an as-yet-unidentified genetic susceptibility (which in Dr. Huq's opinion likely underlies the dysfunction) interacts with environmental stressors, such as inflammation, cytokine activation, or some sort of immune activation. *Id* at 104-06. In this case, Dr. Huq proposed, R.A. did not suffer from a recognized mitochondrial disease, but instead a less severe form of mitochondrial dysfunction that was still significant enough to precipitate his subsequent developmental problems. *Id.* at 95.

Dr. Huq's conclusion that R.A. has underlying mitochondrial dysfunction was based not on a defined set of clinical criteria[23], but instead on a number of overlapping factors, including R.A.'s clinical history and treater opinions, which were in turn the product of extensive lab work and related testing and which Dr. Huq deemed relevant. Dr. Huq specifically pointed to the following aspects of R.A.'s clinical history as supportive of his determination: (1) dysfunction of the central nervous system, (2) gastrointestinal system (diarrhea) problems, (3) musculoskeletal system issues (hyperextensibility), and (4) liver dysfunction (as evidenced by elevated liver enzymes). Tr. at 112-13, 126-31.

Dr. Huq cited different components of the record to substantiate each of these clinical factors. With respect to the first three, he primarily relied on a mix of anecdotal evidence and parent testimony. Thus, Dr. Huq's determination that R.A. suffered from severe gastrointestinal problems was derived less from an individual treater diagnosis or evidence of a severe problem resulting in medical intervention, than from the Andersons' individual reports that R.A.'s diarrhea was out of the ordinary and their documented efforts to have it treated by his pediatricians. *See* Tr. at 41-42; Huq Rpt. at 2; Pet'rs' Exs. 6 at 27 and 8 at 1. He similarly concluded that R.A.'s purported hyperextensibility was clinically significant, although he referenced no treater determination reaching that conclusion, or

[22] As explained by respondent's expert, Dr. Cohen, Leigh Disease is a progressive neurometabolic disorder generally manifesting in infants that are born healthy but thereafter show severe, progressive deterioration in neurological function following a fever or viral illness, ultimately resulting in death. *See* Tr. at 215.

[23] Because of the overlapping factors involved in diagnosing mitochondrial dysfunction, Dr. Huq testified, he does not rely on fixed criteria, such as what is referred to as the "Walker" or "Modified Walker" Criteria. Tr. at 170-71. These criteria are diagnostic guidelines, based upon published medical literature, for evaluating whether a child suffers from some kind of mitochondrial disease through application of a point system for various symptoms or test results observed in the diagnosed patient. *Id.* at 272-73; *see also* Ulrich A. Walker et al., *Respiratory Chain Encephalomyopathies: A Diagnostic Classification*, Eur. Neurol. 36:260-67 (1996).

medical record in which such a condition was acknowledged or underscored as particularly debilitating.[24] As evidence of nervous system dysfunctionality, Dr. Huq pointed (reflexively) to R.A.'s autism diagnosis. Tr. at 112, Huq Supp. Rpt. at 1. He also noted that R.A. had been diagnosed with absence seizures, another central nervous system problem likely related to mitochondrial dysfunction. Tr. at 112, Huq Supp. Rpt. at 1.

Dr. Huq also considered what he referred to as "bioclinical abnormalities," or indirect markers of mitochondrial dysfunction. Tr. 95, 113. These "abnormalities" were first described in tests conducted over a large period of time in R.A.'s life, from 2001 through 2010, many of which were primarily performed by Dr. Shoffner, and which included metabolic evaluations of R.A.'s liver enzymes, ammonia levels, lactic acid levels, and carnitine. See generally Pet'rs' Ex. 13 at 22-26, 134, and 961. Notably, these tests were not performed around the time when R.A. was allegedly experiencing the vaccine-induced onset of developmental problems, but instead years later – and after R.A. had been diagnosed with autism. Tr. at 95, Pet'rs' Ex. 9.[25] The biochemical abnormalities Dr. Huq cited as relevant included mildly elevated lactate levels (Tr. at 134), low free and total carnitine levels (Tr. at 113), multiple amino acids in the urine (Tr. at 113-14), and elevated liver enzymes (Tr. at 125-29). Dr. Huq also cited to evidence of elevated ammonia levels that fluctuated with normal values over a period of three years as indicative of mitochondrial dysfunction. Tr. at 117-18.

However, Dr. Huq's conclusions were based on results that varied widely throughout the history of R.A.'s clinical testing. Dr. Huq addressed the inconsistency of such results, explaining that some of the abnormal results were not replicated in later tests. Tr. at 114 (stating "ideally you want [abnormal test results] to be repeated many, many times…. Often, I have patient[s] where I have molecularly proven mitochondrial disorder, and I will get abnormality in one visit, and I will not get abnormality in other visit."). However, he downplayed the significance of the conflicting results, emphasizing that the body's compensatory mechanisms adjust and equilibrate enzyme pathways to normalize values regardless. Tr. at 113-16.

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[24] Thus, as noted above, during a January 2001 pediatric visit R.A.'s purported "loose joints" were briefly mentioned but not identified as having any negative effects on his overall health. Pet'rs' Ex. 3 at 17, 18.

[25] The fact that all biomarker tests were performed so long after the alleged onset of R.A.'s developmental problems was not deemed by Dr. Huq as diminishing the value of the testing. In his view, later-acquired laboratory results could still reflect an individual's physiological status during an earlier period of life, because when a biomarker is consistently abnormal over a period of time it is reasonable to assume that the source of dysfunction originates within the individual's body, rather than as the product of a transient external factor. Tr. at 200-01.

Dr. Huq also did not deny the inconclusive or negative quality of some of the other testing performed on R.A. relevant to the mitochondrial disorder diagnosis. Thus, he acknowledged that there was no evidence of any genetic cause for R.A.'s purported mitochondrial dysfunction. Tr. at 205. He agreed as well that while the muscle fiber abnormalities revealed in Dr. Shoffner's testing could be evidence of mitochondrial dysfunction, they could also simply be evidence of a nascent susceptibility to dysfunction, making it difficult to place too much confidence in this category of testing. *Id.* at 136.

Moving on from testimony about R.A.'s purported underlying mitochondrial dysfunction, Dr. Huq opined on the impact the MMR vaccine could have on a similarly-situated child. As Dr. Huq testified, R.A.'s developmental injury began with administration of the MMR vaccine, which induced a response that initiated a cascade of events, leading to inflammation, exacerbated by immune dysfunction (as well as mitochondrial dysfunction), and culminating in R.A.'s subsequent development of mild autism. Tr. at 140, 163. Specifically, Dr. Huq explained how mitochondrial dysfunction could be triggered or worsened by a variety of external environmental stressors, such as inflammation or immune activation, that could in turn produce reactive oxygen species. *Id.* at 102. When such external environmental stressors interacted with mitochondria susceptible to damage due to underlying genetic mutation (as was alleged to have been the case here), the external stressors could trigger a condition resembling, if in milder form, a more well-observed monogenic mitochondrial disease or disorder. *Id.* at 99-103.

In this case, Dr. Huq maintained, the febrile illness R.A. experienced after the MMR vaccine was the initial triggering external factor. Fever caused the production of inflammatory cytokines that produce reactive oxygen species. Tr. at 142. The reactive oxygen species, in turn, could lead to further production of free radicals, and further impair mitochondrial and immune function. *Id.* at 142, 175. In addition, Dr. Huq claimed that the MMR vaccine was itself immune-suppressive. The result, according to Dr. Huq, was a cyclical process impairing mitochondrial function and overall immune function, and ceasing only when vulnerable cells were eliminated or when the body's compensatory mechanisms equilibrated the body. *Id.* at 140-42.

Despite putting forward this theory, however, Dr. Huq struggled to identify evidence from the record substantiating it. Thus, he pointed to little from R.A.'s medical history evidencing the inflammatory/immunologic cascade he proposed had been triggered by the MMR vaccine – whether a contemporaneous treater diagnosis or testing that would

corroborate his theory.[26] Instead, he primarily relied on the fact that, in the six months after the December 1999 vaccination, R.A. had been taken to the pediatrician multiple times for URIs or other viral illnesses, citing this pattern as proof of an ongoing linked process (a determination that R.A.'s own treaters did not themselves make at the time). Tr. at 95.

Importantly, Dr. Huq conceded that the nature of R.A.'s injury was not as his report had suggested. Thus, as he agreed on cross-examination, the contemporaneous medical records from six days, eight days, six months, and even nine months after R.A.'s vaccination did not in fact suggest that R.A. had experienced a regression in prior-acquired skills or language, and that he was unaware of evidence to the contrary. Tr. at 177-85, Pet'rs' Ex. 3 at 6. He therefore admitted that "my use of the term 'regression' [in the expert report] was not – was not probably appropriate." Tr. at 185.

To support the theory of the triggering impact of a vaccine on a child with preexisting mitochondrial dysfunction, Dr. Huq relied heavily on three studies: Jon S. Poling, et al., *Developmental Regression and Mitochondrial Dysfunction in a Child with Autism,* J. Child Neurol. 21(2) 170-72 (2006), filed as Pet'rs' Ex. 27 Tab N ("Poling"); John Shoffner et al., *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression,* J. Child Neurol., 25:429-34 (2010), filed as Pet'rs' Ex. 27 Tab P; ("Shoffner"); and Weissman, et al., Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis, PLoS ONE 3(11): e3815 (2008),[27] filed as Pet'rs' Ex. 27 Tab T ("Weissman"). Huq Rpt. at 3, Tr. at 189-90.

Dr. Huq referenced the Poling case involving a 19-month-old child who, "Within 48 hours of vaccination [] was inconsolable, crying, irritable, lethargic, and refused to walk," and who could not walk up stairs at all four days later. Poling at 171. Dr. Huq testified that there was a striking similarity between the time course of the abnormality described in Poling and R.A. Tr. at 144. However, the distinctions between Poling and R.A.'s

[26] The decisions of this tribunal undermine the component of Dr. Huq's opinion connecting R.A.'s repeated URIs and related health problems to the alleged immunologic process that led to his autism. Thus, Dr. Huq's suggestion at hearing that the MMR vaccine has immunosuppressive qualities (Tr. at 141-42) was facially not well founded (at least in instances where autism is the alleged injury). That theory was thoroughly evaluated, and discredited, in prior decisions in cases alleging that a vaccine produced autism. *See Snyder v. Sec'y of Dept. of Health and Human Services,* No. 01-162V, 2009 WL 332044, at *102-04 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 706 (2009) *(*evidence demonstrating that measles vaccines are routinely given to children with challenged or compromised immune systems, without harmful effects, undercuts the theory that the vaccine virus is immunosuppressive or leads to viral persistence).

[27] Weissman (which the hearing transcript erroneously refers to as "Weizman" (Tr. at 193) was submitted twice in this case – first as Petitioners' Exhibit 27, Tab T, and then as Exhibit 29, Tab P. Hereinafter I shall cite only to the Exhibit 27 copy.

circumstances were more evident – for, as Dr. Huq conceded at trial, not only did R.A. not experience any developmental regression, but his developmental delays were evident only months after the vaccination as opposed to days, and the severity of his delays or motor difficulties was not comparable either. *Id.* at 144, 191-192.

Shoffner (authored by the same Dr. Shoffner who treated R.A. in 2008) involved a retrospective chart review of 28 individuals diagnosed with both mitochondrial disease and ASD. Nearly a third of the studied individuals (17 of 28) experienced developmental regression, and nearly 71 percent of that subset regressed after fever (although the precise extent and duration of fever for each subject were unknown, as the study relied wholly on parental reports of fever rather than clinically-confirmed data, making that variable unreliable scientifically). Further, the clinical situation described in Shoffner involved regression within a two-week window following a vaccination. Dr. Huq proposed that there was a "similar mechanism or similar pathophysiology" in this case, rendering Shoffner relevant. Tr. at 146. Like Poling, however, Shoffner dealt with regression rather than the mere development of autism manifesting as delayed development. Further, Shoffner itself undermined the weight Dr. Huq placed upon it, since its authors explicitly recognized that their study found no relationship between vaccination and the observed regression. Shoffner at 432 ("the vaccines did not appear related to the neurologic regression").

Dr. Huq further relied on Weissman as providing an analog to R.A.'s own experience. Huq Rpt. at 6. Weissman was a retrospective review of the medical histories of 25 ASD-diagnosed patients who also had identifiable mitochondrial disease or dysfunction, and argued that "defective mitochondrial oxidative phosphorylation is an additional pathogenetic basis for a subset of individuals with autism." Weissman at 5. But this article, like Poling and Shoffner, mainly involved individuals who had unquestionably experienced some form of developmental regression or markedly delayed early motor milestones. Weissman at 3. Further, as Dr. Huq admitted, of the 25 individuals studied, only *one* had suffered neurodevelopmental deterioration following vaccination – the child described in Poling. Tr. at 194.

In addition to offering scientific literature intended to directly support Petitioners' theory, Dr. Huq offered a variety of other literature intended to "fill in the blanks" – in particular, by suggesting a broader relationship between mitochondrial disorders and autism, independent of whether a vaccine could trigger a reaction in a child with preexisting mitochondrial dysfunction. In particular, he referenced several pieces of literature involving brain tissue studies in which associations between those regions of the brain responsible for behaviors affected by autism and mitochondrial dysfunction were

examined. *See generally* A. Anitha, et al., *Brain Region-Specific Altered Expression and Association of Mitochondria-Related Genes in Autism,* Molecular Autism, 3:12, 1-12 (2012), filed as Pet'rs' Ex. 44 ("Anitha"); Abha Chauhan, et al., *Brain Region-Specific Deficit in Mitochondrial Electron Transport Chain Complexes in Children with Autism*, J. Neurochem., 117:209-20 (2011), filed as Pet'rs' Ex. 45 ("Chauhan"); and Guomei Tang, et al., *Mitochondrial Abnormalities in Temporal Lobe of Autistic Brain*, Neurobiology of Disease 54:349-61 (2013), filed as Pet'rs' Ex. 46 ("Tang").

Anitha explored gene expression and genetic association of specific genes related to mitochondrial functions by testing postmortem brain tissue samples taken from eight autistic patients, and showed altered gene expression in the examined brain regions. Anitha at 1; Tr. at 147. As Dr. Huq explained, Anitha showed abnormalities of mitochondrial gene expression and abnormal activity in those brain regions associated with social communication and language function – the same regions from which the pattern of language dysfunction exhibited by R.A. would also be expected to arise. Tr. at 147-49. However (and as Dr. Cohen later emphasized), the tissue samples studied in Anitha may have been compromised, yielding questionable results. Tr. at 375-78. More significantly, the genes which showed altered expressions in Anitha were not indicated (based upon testing performed in December 30, 2013 by Dr. Kendall) as altered in R.A. *Compare* Pet'rs' Ex. 25 (reporting R.A. exhibited genetic variants only in the BRWD3 gene and the AUTS2 gene) *with* Anitha at 5 (genes with altered expression in studied postmortem brain tissue samples did not include either the BRWD3 or the AUTS2 gene).

Chauhan examined levels of mitochondrial proteins in postmortem frozen brain tissue samples from brain regions of subjects with autism, finding that abnormalities in mitochondria leading to oxidative stress and abnormal energy metabolism may play some role in autism's general etiology. Chauhan at 209, 217. Dr. Huq testified that Chauhan, like Anitha, showed mitochondrial dysfunction in the frontal lobe, cerebellum, and temporal lobe, and the presence of reactive oxygen species that could encourage additional dysfunction in children with autism. Tr. at 150. Chauhan, however, suffered from some of the same sample source deficiencies that characterized Anitha.[28] Tang examined mitochondrial proteins in frozen brain tissue samples taken from autistic

[28] Thus, as Dr. Cohen later argued in his testimony, the tissue samples studied in Chauhan (like those in Anitha) may have been compromised, given that the subjects from which the samples were derived had died from seizure or drowning. Tr. at 375-78; *see also* Chauhan at Table S1 available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4839269/bin/NIHMS593243-supplement-supplemental_info.pdf (last visited October 31, 2016). This is because, as Dr. Cohen explained, mitochondria rapidly degrade after brain tissue reaches room temperature, which would inevitably occur since the tissues were derived from deceased individuals.

subjects, and reported mitochondrial defects within the temporal cortex of autistic subjects compared to controls. Tang at 356. Dr. Huq characterized the defects discussed in Tang as a complex dysfunction that he "would expect from a gene-environment interaction or external stressors." Tr. at 151.

C. Respondent's Expert—Bruce Cohen, M.D.

Dr. Cohen submitted an expert report and testified at hearing. Tr. at 206-403; Ex. A, Expert Report of Bruce H. Cohen, M.D., dated February 5, 2015 (the "Cohen Rpt.") Dr. Cohen's testimony attempted to directly rebut Petitioners' assertion that R.A. suffered from a mitochondrial disease or disorder of some kind related to his alleged post-vaccination developmental regression.

Dr. Cohen graduated from Albert Einstein College of Medicine of Yeshiva University in 1982 (after completing his undergraduate degree at Washington University in St. Louis). Cohen Rpt. at 1. He went on to complete a pediatric residency at Children's Hospital of Philadelphia, followed by a pediatric neurology residency at the Neurological Institute of New York and Babies Hospital of Columbia Presbyterian Medical Center, and a pediatric neuro-oncology fellowship at the Children's Hospital of Philadelphia. *Id.* Dr. Cohen is board-certified in neurology, with special competence in child neurology, and has in the past been board-certified in pediatrics. Ex. B at 2.He is currently the Director of Neurology at the Children's Hospital Medical Center of Akron, and a Professor of Pediatrics at Northeast Ohio Medical University, where he teaches general pediatric neurology to medical students, residents, and fellows. Resp't's Ex. B at 2; Tr. at 207-08.

Dr. Cohen has demonstrated experience in studying mitochondrial diseases and related metabolic disorders. He has also taught courses specifically on mitochondrial disease in symposia. Resp't's Ex. B at 5. He is a reviewer for several journals, and serves on the editorial board for the *Mitochondrion and the Pediatric Neurology Journal*. *Id.* at 3. He also serves on various review committees, including the Neurofibromatosis Consortium. *Id.* In addition, Dr. Cohen has written extensively on issues of mitochondrial diseases, authoring or co-authoring nearly 25 peer-reviewed articles on the topic. *Id.* at 35-40. Dr. Cohen has served in many different capacities for the United Mitochondrial Disease Foundation since 1999 and served on many different committees involving the topic of mitochondrial disease. *Id.* at 3-4.

Dr. Cohen's expertise on the topic of mitochondrial diseases and disorders includes treatment of patients with the condition for the past 22 years. Tr. at 208. Roughly 75 percent of Dr. Cohen's clinical practice concerns mitochondrial patients, amounting to

thousands of patients over the past 15 years. *Id.* at 208-09. He routinely diagnoses mitochondrial diseases or dysfunction in his patients, estimating that in the past 22 years he has seen several thousand patients in which the disease was suspected, or actually diagnosed. *Id*. Although Dr. Cohen does not diagnose ASDs, some of his patients have autism as well as suspected mitochondrial diseases. *Id.* at 209-10.

Dr. Cohen formulated his opinion after reviewing R.A.'s medical records and objective data plus the expert reports and journal articles filed. Cohen Rpt. at 8. Based on this review, Dr. Cohen disagreed with Dr. Huq's conclusions, and opined instead that there is no credible evidence that R.A. has a mitochondrial illness, or that any vaccination R.A. received in any way contributed to his autism or other medical conditions. Cohen Rpt. at 10; Tr. at 213.

Dr. Cohen began by providing background on the difference between mitochondrial disorder and dysfunction, defining those terms to mean primary and secondary mitochondrial diseases, respectively. Tr. at 217. Primary mitochondrial disease results from pathogenic mutations in genes that regulate mitochondrial function. *Id*. at 217. Patients with a primary mitochondrial disease affecting Complex I function are devastatingly ill, with symptoms including loss of vision, dystonia, severe encephalopathy classified as Leigh or Leigh-like disorders, and death. *Id.* at 215-16. In contrast, secondary mitochondrial disease refers to impairments to mitochondrial function that do not result from pathogenic gene mutations. *Id*. Secondary mitochondrial disease may be triggered by environmental stimuli, such as chemotherapy or poisons. *Id.* 218, 271-72, 399-400.

Dr. Cohen's opinion that R.A. does not have mitochondrial disease or dysfunction was derived from review of R.A.'s medical history, contrasting what he saw in it to assumptions Dr. Shoffner had made about that history when he treated R.A. in 2008.[29] First, Dr. Cohen emphasized, it was readily evident to him that R.A. was not suffering from a primary mitochondrial disease. He described the clinical presentation of mitochondrial disease, which would include dementia, strokes, ataxia, abnormal MRI scans, cardiomyopathy, myopathy, cirrhosis, loss of night and color vision, hearing loss, and other progressive symptoms – none of which were present for R.A. Tr. at 244-47. Genetic testing performed on R.A. was largely inconclusive as well, showing the presence of some mutations but nothing that would establish a known form of primary mitochondrial disease. *Id.* at 239.

[29] In discussing the clinical guidelines used to diagnose a mitochondrial disease or dysfunction, Dr. Cohen testified that (like Dr. Huq), he does not always use the Walker criteria to diagnose mitochondrial disease, and instead prefers genetic testing as the most reliable indicator that disease is present. Tr. at 238-39, 285.

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Second, Dr. Cohen noted that there was insufficient record evidence that R.A. even suffered from a lesser, secondary mitochondrial disease. In this case, Petitioners allege a neurologic injury as the prompt for R.A.'s developmental problems, and therefore damage to R.A.'s brain tissue should have been evident on MRI scans. Tr. at 319-20. Here, however, not only did R.A. not exhibit common neurological symptoms, but his MRI scan was normal. *Id.* at 246. In addition, while mitochondrial disease can lead to multisystem involvement (as Dr. Huq had suggested was evident in R.A.'s case), the clinical presentation for R.A. did not support the conclusion that multisystem failure was present. See Cohen Rpt. at 9. Thus, Dr. Cohen took issue with Dr. Huq's reliance on evidence of R.A. suffering from chronic diarrhea as proof of a gastrointestinal failure evidencing a mitochondrial disorder. In Dr. Cohen's view, patients suffering from even secondary mitochondrial disease would experience something more demonstrably severe, such as horrible constipation, rather than what R.A. is reported to have suffered. *Id.* at 244-45.[30]

Dr. Cohen also questioned the strength of Petitioners' assertions that R.A.'s purported absence seizures evidenced a central nervous system manifestation of an underlying mitochondrial disorder. The EEG from the medical records showed a three second episode of a three-per-second spike and wave. However, as Dr. Cohen testified, absence seizures can occur in generally healthy children, and are typically diagnosed only after an EEG shows more than one episode of spike and wave, and usually lasting more than three seconds. *Id.* at 221-22. Further, if absence seizures were a concern, additional EEGs would have been sought for R.A. but this did not occur. *Id.* at 223. Dr. Cohen therefore discounted the accuracy of Dr. Huq's conclusion that R.A. had ever suffered from absence seizures at all.

Dr. Cohen next noted inaccuracies in Dr. Shoffner's factual assumptions about R.A.'s medical history. Dr. Shoffner's assessment was based in part on the proposition that R.A. had experienced a regression in his development. A regression of skills at 17-18 months of age, according to Dr. Shoffner, is a clinical indicator of mitochondrial dysfunction. *Id.* at 220; Pet'rs' Ex. 9 at 42. However, R.A. never in fact showed signs of regression – something, as noted above, that Dr. Huq conceded. *Id.* at 220.

Similarly, Dr. Shoffner had assumed that R.A.'s onset of his developmental problems was contemporaneous with the fever he had experienced in the six days following his receipt of the MMR vaccine (which presumably caused the fever). Tr. at 220.

[30] Dr. Cohen also proposed, as an alternative explanation, that R.A.'s chronic diarrhea could have been the result of R.A.'s treatments, like IVIG. Tr. at 244.

Such an assumption was consistent with Dr. Shoffner's proposals about the relationship between fever and developmental regression. Shoffner at 430 ("[a] relationship between fever and autistic regression is defined as regression beginning within 2 weeks of a febrile episode without the suggestion of infectious meningitis or encephalitis"). Yet in this case, as the medical records revealed,[31] R.A.'s developmental problems had manifested no earlier than five to six months after the MMR vaccination - not within the two-week window that Dr. Shoffner's own article said would be expected if fever had been the triggering factor. *Id.* at 220-21. Dr. Cohen also opined that the febrile illness R.A. exhibited was most likely caused by a rhinovirus rather than the MMR vaccine, given what the medical records showed. *Id.* at 363.

Dr. Cohen went on to review Dr. Shoffner's medical evaluation of R.A., and in particular the testing that Dr. Huq relied on as supporting evidence of a probable Complex I mitochondrial defect. Pet'rs' Ex. 10 at 27-30; Tr. at 224-44. Dr. Cohen opined that the metabolic, biochemical, and genetic laboratory test results generated in R.A.'s case did not support a diagnoses of mitochondrial disorder. He specifically considered each relevant testing component in reaching this conclusion.

First, Dr. Cohen challenged Dr. Shoffner's conclusions that testing revealed R.A. had an elevated lactic acid level sufficient to establish the existence of secondary mitochondrial disease. As Dr. Cohen explained, lactic acid readings alone are insufficient for a mitochondrial dysfunction diagnosis, because elevated levels can occur in otherwise healthy individuals simply when a patient struggles during the sampling procedures. Tr. at 227. This is particularly true with autistic children, where "it's hard to get a normal blood lactate because, in fact, there is often a struggle, and there is certainly the use of a tourniquet." *Id.*; Cohen Rpt. at 9. For an elevated lactate reading to be meaningful, Dr. Cohen maintained, it must be correlated with a concomitant amino acid draw showing elevated alanine. *Id.* at 225, 227. But in R.A.'s case, alanine levels tested as normal. Lactate levels can also fluctuate widely in different clinical settings, and can actually drop when certain patients clinically worsen, further reducing their value as a diagnostic tool. *Id.* at 338-39. Overall, Dr. Cohen stated, lactate readings were being viewed as less and less helpful to experts in the field of mitochondrial disease study, given all the limitations of such testing. Tr. at 227, 338-39.

Dr. Cohen next discussed the amino acid test results from R.A.'s urine samples that had led Dr. Shoffner to conclude that R.A. possibly had proximal renal tubular

[31] Of course, Petitioners contend that R.A. manifested developmental problems far closer to the time of his vaccination. However, and as I discuss in greater detail below, such contentions are not corroborated by the contemporaneous fact record, and I therefore give them less evidentiary weight.

acidosis. In Dr. Cohen's view, some of the nutritional or vitamin supplements R.A. was taking at the time, which included amino acid supplements of taurine, 3-methyl glycine, and cysteine, could artificially elevate amino acid levels. Tr. at 228.[32] Moreover, the normal levels of amino acids found in R.A.'s cerebral spinal fluid suggested instead that his amino acids were not high, but that his kidneys were instead appropriately flushing excess amino acids introduced into R.A.'s body by the variety of supplements he was then taking (which explained the urine testing results). *Id.* at 228-29. Thus, Dr. Shoffner placed too much reliance on the urine test results, while ignoring contrary but relevant results that did not corroborate the conclusion that R.A. suffered from renal tubular acidosis. *Id.*

Dr. Cohen further opined that R.A.'s muscle biopsy results were similarly unsupportive of Dr. Shoffner's diagnostic conclusions. In reviewing the relevant testing, Dr. Cohen acknowledged that R.A.'s muscle histology as reviewed under the light microscope was abnormal, but otherwise not indicative of a mitochondrial dysfunction. Tr. at 229-30, Cohen Rpt. at 9. Further, the immunohistochemistry tests did not show any features of mitochondrial illness, specifically ragged red or blue fibers, COX negative fibers, or excessive staining on whole and panel stains. *Id.* at 230-32.

Dr. Cohen next discussed Dr. Shoffner's enzymology testing. Such tests isolated mitochondria from R.A., and then evaluated each of four protein complexes that typically work in conjunction to produce energy in heathy cells. Tr. at 233. Dr. Shoffner had relied on R.A.'s phosphorylation enzymology results to conclude that he suffered from a Complex I defect. See Pet'rs' Ex. 9 at 42. But Dr. Cohen proposed that the testing was too incomplete to support that conclusion. Dr. Shoffner had conducted two separate tests for Complex I and Complex IV, but only one of each returned abnormal results. *Id.* at 393-94, Pet'rs' Ex. 9 at 24. Thus, Dr. Cohen questioned whether the abnormal results were truly reliable.

More significantly, in Dr. Cohen's view, Dr. Shoffner had failed to standardize the results against a marker enzyme called citrate synthase – an essential step, in Dr.

[32] As noted previously, at hearing Dr. Cohen proposed that Dr. Shoffner had failed to take into account the role of these supplements in skewing the amino acid level test results of R.A.'s urine. Tr. at 228, 345, *see also* Pet'rs' Ex. 10 at 16-17. In fact, the medical record indicates that Dr. Shoffner recognized that R.A. was at the time taking 975 mg of taurine. *See* Pet'rs' Ex. 10 at 17. It does not, however, similarly reveal that Dr. Shoffner took account of the possibility that other supplements (like 3-methyl glycine or cysteine) could have affected R.A.'s amino acid counts. Overall, I find that the record is too ambiguous on this point to determine that the amino acid test results alone are incorrect, or should be discounted along the lines proposed by Dr. Cohen. At the same time, however, given the weight of the other test results, I do not find the positive amino acid test results to be particularly probative in support of Petitioners' contention that Dr. Shoffner's diagnosis is trustworthy from an evidentiary standpoint.

Cohen's opinion, when evaluating a muscle enzymology result. *Id.* at 235-37, Cohen Rpt. at 10. As Dr. Cohen explained, citrate synthase is an important marker enzyme in the mitochondria that provides a proxy measurement of mitochondrial content in the muscle, and thus helps confirm the success rate of the extraction process when testing. Cohen Rpt. at 11. Citrate synthase levels are therefore used to standardize mitochondrial enzyme values, "[b]ecause if the citrate synthase is low, your other enzymes are going to be low as well." Tr. at 234. Dr. Cohen performed that standardization himself in preparing his expert opinion, relying on recognized diagnostic criteria for evaluation of mitochondrial disease as well as the citrate synthase levels measured by Dr. Shoffner at the time. *Id.* at 233-35. In so doing, Dr. Cohen found that R.A.'s enzyme function was either normal or only slightly above normal. *Id.;* Cohen Rpt. at 9-10. According to Dr. Cohen, the remaining enzymology results were normal, and therefore there was "just zero evidence … that this child ha[d] a Complex I defect." Tr. at 235.

Dr. Cohen also reviewed the testing of R.A.'s ammonia levels, which Dr. Huq had deemed significant because high levels of ammonia can be a biomarker of mitochondrial dysfunction. Tr. at 117-18. In Dr. Cohen's view, the ammonia testing results were too fluctuating to support a diagnosis of mitochondrial disease, or were otherwise too close to the normal range to be alarming. Tr. at 240-42. Rather, Dr. Cohen attributed R.A.'s slightly elevated ammonia to the amino acid supplements he was taking. *Id.* at 241. Dr. Cohen did, however, acknowledge the presence of ammonia level test results for R.A. at various times that did support Petitioners' argument. *Id.* at 342.

Dr. Cohen took a similar view of the liver enzyme levels observed in Dr. Shoffner's testing – in particular, AST and ALT. As Dr. Cohen explained, chronically elevated liver enzymes can be an indication of specific mitochondrial disease, such as Alpers disease. Tr. at 242-43. R.A.'s liver enzymes, however, exhibited periodic rises, but then returned to normal, which would not occur in individuals with primary or secondary mitochondrial disease. *Id.* at 243. And certain drugs and supplements R.A. was ingesting were known to elevate ALT levels, including Solu Cortef, Solu Medrol, and IVIG. *Id.* at 241-42, 342-43.

Dr. Cohen also discussed some of the broader aspects of Dr. Huq's causation theory. In particular, he disputed the significance of R.A.'s post-vaccination illnesses from the winter and spring of 2000 as evidencing multisystem inflammation – according to Dr. Huq, proof of the interaction of his alleged secondary mitochondrial disease and his immune system. To Dr. Cohen, nothing in R.A.'s medical record corroborated this view. Tr. at 249-50. Rather, the infections and pediatric illnesses R.A. had experienced in this time period were not unusual for an otherwise healthy child of the same age. *Id.* at 251,

369-70. Indeed, individuals with demonstrated inborn metabolic errors, or even primary mitochondrial disease, do not typically exhibit significant sequela from vaccinations, further reducing the significance of R.A.'s purported progressive susceptibility to infection. *Id.* at 252.

Finally, Dr. Cohen questioned Dr. Huq's proposal (based on Anitha and similar studies examining post-mortem brain tissue of autistic individuals) that autism could be causally associated with mitochondrial disease or dysfunction. Tr. at 147-51. In Dr. Cohen's view, such papers were fundamentally flawed because the marker molecules they tested for, which revealed Complex I and Complex IV activity, would disappear rapidly after brain tissue reaches room temperature (which would inevitably occur since the tissues were derived from deceased individuals), rendering their conclusions unreliable. Tr. at 375-78. Further, while the articles indicated there was a change in the mitochondria in the subjects' brains, Dr. Cohen testified there is no real understanding of why this occurs, rending the studies of little probative value and "not relevant to [R.A.]." *Id.* at 377-78.

III. APPLICABLE LEGAL STANDARDS

A. Evidentiary 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). Petitioners are not asserting a Table claim in this case.

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 causation-in-fact claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005): "(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."

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, 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 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)). But this does not negate or reduce a petitioner's ultimate burden to establish his 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).

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 against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), aff'd, 463 Fed. 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; S*hapiro 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 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 Fed. 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*, 23 Cl. Ct. at 733). Ultimately, a determination regarding a witness's credibility is often 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 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, a special master may consider whether the expert is offering an opinion that exceeds the expert's 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) all testimony of the experts offered at the entitlement hearing was heard and considered, a special master 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).

D. Mitochondrial Disease and Dysfunction

As my recitation above of the testimony by the experts at hearing reveals, the function of mitochondria in the human body is highly pertinent to Petitioners' case (and particularly their causation theory). The mitochondria are cellular organelles that are present in the body's cells and are primarily responsible for creating energy. Dorland's

Illustrated Medical Dictionary 61 (32nd ed. 2012); Tr. at 98. Mitochondrial dysfunction, according to Dr. Huq, is a loosely used term for conditions that result from mitochondria not properly functioning. Tr. at 104. Mitochondrial disease can manifest with a multitude of symptoms, including dysfunction of the central nervous system, gastrointestinal system, and musculoskeletal system. Tr. at 112. Mitochondrial disease can also manifest through altered biochemical and clinical abnormalities, such as elevated levels of certain amino acids and biomarkers like lactic acid. Tr. at 111. But it can be difficult to diagnose mitochondrial disease given the variety of possible symptoms and the lack of a reliable and agreed-upon diagnostic biomarker. *Id*. at 102-03; 114; 214-18.

Although there is a distinction between primary mitochondrial disease and secondary, the parties largely do not dispute that only the secondary form (in which mitochondrial dysfunction is the product of some kind of environmental, external stimuli, rather than directly the result of an underlying genetic mutation) is applicable to R.A.'s claim. Tr. at 101-03, 169, 217-18.

ANALYSIS

I. R.A. Does Not Suffer from Mitochondrial Dysfunction

The central deficiency in Petitioners' case is their inability to establish by preponderant evidence that R.A. actually had some form of secondary mitochondrial disease. The medical record does not support that conclusion, and the treater opinion and testing results relied upon for the diagnosis are either based on demonstrably incorrect assumptions or inconclusive evidence. Because Petitioners' claim is dependent on this finding, the entirety of their causation theory cannot stand.

An important point right off the bat is not disputed: R.A. did not suffer from a primary mitochondrial disease. As a result, Petitioners concede that the kind of obvious symptoms associated with the more well-recognized forms of mitochondrial disease are absent, leading them to propose that a variety of lesser evidence in the medical record supports their theory. Petitioners rely heavily on R.A.'s immediate post-vaccination illness and medical history in the subsequent months.

That evidence, however, is at best inconclusive, and otherwise provides weak support for evidence of mitochondrial dysfunction. There is no testing from the period in which R.A. would have been experiencing a vaccine reaction that would confirm he possessed any mitochondrial dysfunction. R.A.'s frequent trips to the pediatrician in the first half of 2000 are more suggestive of the variable health of an infant than that of a child

experiencing progressive symptoms inexorably leading to a cessation of language or motor development. No contemporaneous treaters thought otherwise; none proposed that the URIs or other symptoms for which R.A.'s parents sought treatment were evidence of a greater medical issue. Moreover, Dr. Huq's attempts to characterize certain of R.A.'s symptoms – for example, his diarrhea – as components of some multisystemic failure reflecting mitochondrial dysfunction are unpersuasive, inflating a less severe gastrointestinal problem that was more likely as not attributable to other factors into an alarming warning sign. The same is true of Dr. Huq's claims that R.A.'s autism[33] or purported seizure disorder (the latter being especially unsupported by the record) evidence central nervous system failure.

In addition, the conclusion that R.A. did have some kind of mild secondary mitochondrial disease is largely the product of Dr. Shoffner's treatment in 2008. Putting aside the fact that he treated him long after the vaccination, the test results that Dr. Shoffner relied upon in part for his conclusion are not robust or trustworthy enough to find it "more likely than not" that R.A. possessed mitochondrial dysfunction. Thus, as Dr. Cohen persuasively established, the lactic acid test results were untrustworthy, and would under more generally accepted diagnostic approaches today be deemed of far less utility in evaluating the presence of mitochondrial dysfunction. Tr. at 227. More significantly, the enzymology testing failed to appropriately standardize results by using the marker enzyme citrate synthase, and positive results were otherwise inconsistent or not replicated. Tr. at 235-37, 393-94; Cohen Rpt. At 10; Pet'rs' Ex. 9 at 24. Otherwise, it is evident that Dr. Shoffner accepted recitations about R.A.'s medical history – in particular, the fact that he had experienced regression – as accurate, applying his own theories as a result about the interaction of fever and regression that are not relevant herein. Pet'rs' Ex. 9 at 42; Pet'rs' Ex. 10 at 15; Tr. at 185, 191-92.

I acknowledge the fact that Dr. Shoffner was one of R.A.'s treaters. But that does not mean that his opinion automatically is entitled to the level of deference and evidentiary weight given to contemporaneous treater records in many Program cases – especially when, as here, he reached his conclusions long after the immediately relevant time period. *Nuttall v. Sec'y of Health & Human Servs.,* 122 Fed. Cl. 821, 832 (2015) ("[t]he reasoning underlying the finding that opinions of treating physicians should be given

[33] It is especially unpersuasive when Program petitioners seeking to prove a child suffering from a mitochondrial disorder was rendered autistic after vaccination point to the autism as proof of causation *R.V. v. Sec'y of Health & Human Servs.*, No. 08-504V, 2016 WL 3882519, at *34 n. 80 (Fed. Cl. Spec. Mstr. Feb. 19, 2016), *mot. for review den'd*, 127 Fed. Cl. 136 (2016). This kind of circular logic underscores the weakness of Petitioners' overall claim.

particular weight does not apply when . . . the treating physician only saw the patient after the injury and based his opinion on the same evidence as relied upon by the retained experts"). Overall, the testing results he obtained were too erratic, with some supporting Petitioners' argument while others did not. And in this case, there is not a rigid set of criteria that call for one diagnostic conclusion depending on how those tests bear out. Dr. Huq himself embraced a more expansive, totality-of-the-circumstances form of diagnosing a secondary mitochondrial disease. Tr. at 104-05. Accepting that approach, I cannot find that the overall picture of R.A.'s condition suggests it more likely than not that he suffered from some kind of secondary mitochondrial dysfunction.

In finding as I do, I am giving Dr. Cohen's testimony more weight than Dr. Huq's, and crediting his interpretation of the record over Petitioners' expert's testimony. But I am appropriately tasked with weighing expert testimony, which includes assessing the relative competencies of competing experts on a given subject matter. *Porter*, 663 F.3d at 1250; *Moberly*, 592 F.3d at 1325–26. Both experts were qualified to offer the opinions they did, but Dr. Cohen is the far more experienced medical practitioner when it comes to the subject of mitochondrial diseases and disorders, with more demonstrable expertise studying, diagnosing, and treating the condition. Although not all of Dr. Cohen's assertions were equally convincing, overall he persuasively established that, based on his own professional experience, R.A.'s history is not that of a child suffering from any form of mitochondrial disease.

II. Petitioners Have Not Satisfied the *Althen Prongs*

Because Petitioners cannot establish the keystone of their argument (as their theory relies on a finding that R.A. had an underlying mitochondrial condition that was negatively affected by the MMR vaccine), their case cannot succeed, and technically I need not evaluate the *Althen* factors. *Lasnetski v. Sec'y of Health & Human Servs.*, No. 14-580V, 2016 WL 5851889, at *21 (Fed. Cl. Sept. 9, 2016). But, in an abundance of caution, I will briefly review each of those factors, in order to demonstrate that the weaknesses of Petitioners' case extended beyond the diagnostic issue presented above.

A. *Althen* First Prong – A Reliable Causation Theory

Petitioners have failed to offer a reliable scientific theory linking the MMR vaccine to autism. Much of the scientific basis for their theory assumes vaccine-induced developmental regression, which it is conceded R.A. did not experience. Accordingly, articles like Shoffner linking fever to regression do not aid their argument. More generally, however, Petitioners have offered little persuasive or reliable support for the proposition

that the MMR vaccine could initiate the "inflammatory cascade" they posit eventually, and over many months' time, result in autism. Indeed, they even rely on discredited concepts, such as the MMR vaccine's alleged immuno-suppressive capacity, to pad out the theory. *See, Snyder v. Sec'y of Dept. of Health and Human Servs.,* No. 01-162, 2009 WL 332044, at *102-4 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 706 (2009) *(*evidence demonstrating that measles vaccines are routinely given to children with challenged or compromised immune systems, without harmful effects, undercuts the theory that the vaccine virus is immunosuppressive or leads to viral persistence).

The component of Petitioners' theory relating to the connection between mitochondrial disease and autism was similarly unreliable. Fundamentally, the literature offered by Dr. Huq does not posit a causal reaction between one and the other, except in cases involving clear primary mitochondrial disease, which R.A. unquestionably did not have. Some of the studies Petitioners offered (in particular, the post-mortem brain tissue studies like Anitha) observe an association between genes related to mitochondrial performance and the areas of the brain linked to functions associated with autism. While these studies individually may not be unreliable[34], they would have to be joined by substantially more corroboration, in the form of additional studies involving live individuals, before they could credibly link autism with a secondary mitochondrial disease sufficient to constitute a reliable theory for purposes of Vaccine Act causation. *See, e.g., Holt v. Sec'y of Dep't of Health & Human Servs.,* No. 05-0136V, 2015 WL 4381588, at *30 (Fed. Cl. June 24, 2015) (explaining that in recent Vaccine Act cases, Federal Circuit judges have expressed concern about special masters' reliance on small studies involving rare events, perhaps because the studies may not be sufficiently powered to detect the events being studied).

More broadly, however, the theory that a vaccine (in particular, the MMR vaccine) could cause autism is one that has been consistently unsuccessful in the Program's history – at least since the time of the Omnibus Autism Proceedings and subsequent decisions.[35] Indeed, as Special Master Hastings noted in the recent *Hardy* decision, to

[34] In addition, some of that same literature may be flawed, as Dr. Cohen pointed out, because it involved the testing for energy-producing organelles found in dead brain tissue. Tr. at 375-78.

[35] The theories were first advanced in proceedings related to the Omnibus Autism Proceeding ("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.

date *every* post-OAP non-Table claim[36] seeking compensation for autism injuries purportedly related to a vaccine that has been tried has failed. *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) (referencing eleven autism claims unsuccessfully tried, plus six that were rejected (over the petitioners' objections) without trial). The same result has occurred in those cases where petitioners claim a child's underlying metabolic disorder (most commonly a mitochondrial disease of some kind) was exacerbated by a vaccine, resulting in a developmental regression or autism itself. *See, e.g.*, *Hardy*, 2015 WL 7732603, at *4-5 (petitioners failed to demonstrate that DTaP vaccine caused or significantly aggravated underlying mitochondrial disease resulting in ASD); *R.V. v. Sec'y of Health & Human Servs.*, No. 08-504V, 2016 WL 3882519, at *42 (Fed. Cl. Spec. Mstr. Feb. 19, 2016), *mot.*

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 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), *aff'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 11 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 the petitioners' claims. These decisions found no persuasive evidence that the MMR vaccine or thimerosal-containing vaccines caused autism. The OAP proceedings concluded in 2010.

[36] In a single instance, petitioners (the parents of a vaccinated child) successfully established a Table injury – an encephalopathy – after vaccination that resulted in an autistic-like developmental regression. *See, e.g.*, *Wright v. Sec'y of Health & Human Servs.*, No. 12-423V, 2015 WL 6665600 (Fed. Cl. Spec. Mstr. Sept. 21, 2015). In *Wright*, the petitioners met the Table criteria for an "acute encephalopathy" following vaccination by establishing by preponderant evidence that the vaccinated child experienced a seizure followed by loss of consciousness shortly after receipt of pertussis-containing vaccine; the severe reaction lasted for more than 24 hours, with resulting demonstrable significant changes in behavior. But the special master responsible for that decision (former Chief Special Master Vowell) explicitly noted in her decision that petitioners would not have been able to establish entitlement under their non-Table claim, because their expert presented a causation opinion that she found "absurd and biologically impossible." *Wright*, 2015 WL 6665600, at *2.

for review den'd, 127 Fed. Cl. 136 (2016) (holding the factual record does not support petitioners' contention that petitioner suffered from a mitochondrial disease or that the flu vaccine had a causal connection to the development of 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 v. Sec'y of Health & Human Servs.*, No. 08-554V, 2015 WL 5443461 (Fed. Cl. Spec. Mstr. July 22, 2015) (petitioners failed to demonstrate that flu vaccine resulted in autoimmune encephalitis).The theory presented in this case was not sufficiently novel or compelling to alter this trend.

B. *Althen* Second Prong – Sequence of Cause and Effect

The record does not allow the conclusion that R.A. experienced any reaction to the MMR vaccine. Unquestionably he experienced a high fever within a week of the vaccination that was sufficiently alarming for his parents to seek emergency care, but it was diagnosed as viral and then resolved. Pet'rs' Ex. 5 at 64. There were no trailing or progressively concerning symptoms thereafter in the next two to three months, and his illnesses in the first half of 2000 were not shown to be linked or associated with a pattern different from what a healthy infant free of developmental problems might also experience. R.A. suffered no demonstrated neurologic injury that could be linked to his subsequent autism diagnosis. R.A.'s autism did not fully manifest for months after, without any evidence of a physiologic process by which it was going to occur. To the extent the Petitioners have attempted to establish onset in late December 1999, their allegations are contradicted by the contemporaneous medical records, which identify nothing about developmental problems for R.A. prior to June of 2000 – six months after vaccination.

I also greatly discount Dr. Shoffner's diagnosis that R.A. did have some form of mitochondrial disease. Not only did he evaluate R.A. nearly eight years after vaccination, but the record reveals that he relied on incorrect facts about R.A.'s history, mischaracterizing the evolution of R.A.'s developmental problem as a regression when there is (as Dr. Huq agreed) no such evidence in the record. The test results Dr. Shoffner relied upon were overall inconclusive and had too much variability to conclude that R.A. suffered from a true metabolic disorder causally related to the MMR vaccine. There is no corroborative diagnosis from any other treaters other than Dr. Huq, whose opinion (based upon the same evidence) was effectively rebutted by Dr. Cohen. The evidence suggests it is more likely than not that R.A.'s autism was idiopathic in origin, rather than caused by the MMR vaccine.

C. *Althen* Third Prong – a Medically Acceptable Timeframe

Viewed loosely, the facts of this case would fit the timeframe that Petitioners urge flows from their theory. Thus, R.A.'s purported inflammatory cascade was triggered within a week of vaccination, and then his symptoms slowly agglomerated (as evidenced by his intermittent infections) until his developmental issues were facially apparent six or more months later. But looked at more carefully, the proposed timeframe does not work, and ultimately reflects the temporal reasoning rejected by controlling precedent. *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014) (holding that "the basis for Ms. LaLonde's petition reduces to a temporal relationship between the administration of the DTaP vaccine and M.L.'s focal brain injuries. As we have stated before, a temporal correlation alone is not enough to demonstrate causation."); *Althen*, 418 F.3d at 1278 (petitioners must show a proximate temporal relationship between vaccination and injury). For even if it is assumed that the MMR could trigger a neurologic injury leading to developmental problems of any kind within a few days to a week after a vaccine was administered, Petitioners' theory does not explain why it would subsequently be expected to take four to six months or more before the developmental side of the injury – the primary injury complained of here – to manifest, without any other obvious physiologic signs. No literature or reliable scientific support was offered to explain why it took so long without any demonstrable change in R.A., and the record itself also provides no illumination of this point.

CONCLUSION

The Andersons plainly love their son, and Mr. Anderson's dedication in attempting to grasp and understand R.A.'s condition was clear to me from his heartfelt testimony, which brought to life R.A. as a person. But the factual record simply does not support Petitioners' contention that the MMR vaccine had any connection to R.A.'s ASD diagnosis, nor have the Petitioners established that the vaccine *could* result in developmental problems in the manner proposed by their theory. The evidence offered, plus the record, is 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.[37]

IT IS SO ORDERED.

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

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