In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 08-504V

(To be published)

R.V. *and* E.V., *parents and natural guardians of* L.V., *a minor*, Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Corcoran Filed: February 19, 2016 Entitlement Decision; Influenza ("Flu") vaccine; Autism Spectrum Disorder ("ASD"); Mitochondrial Disease; Autoimmune Encephalopathy Following Fever or Vaccine.

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

DECISION[1]

On July 11, 2008, R.V. and E.V. filed a petition on behalf of their minor child, L.V. seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program").[2] The Vs sought to establish that the influenza ("flu") vaccine that L.V. received on December 8, 2006, when he was 21 months old, caused an encephalopathy, and/or aggravated L.V.'s alleged underlying mitochondrial disorder, resulting in L.V.'s physiological symptoms and

[1] Because this decision contains a reasoned explanation for my actions in this case, I will post it on the United States Court of Federal Claims website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole decision will be available to the public. *Id*.

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

subsequent developmental regression.

An entitlement hearing was held on April 13-14, 2015, and in the following months 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[3]

A. Birth and Early Medical History.

L.V. was born at term by caesarean section on March 15, 2005, at Abington Memorial Hospital in Abington, Pennsylvania, presenting with no abnormalities. Pet'rs' Ex. 1 at 7, 15-16. L.V. passed his hearing screening on March 16, 2005, and was routinely discharged on March 19, 2005. Pet'rs' Ex. 2 at 4-5, 7. Throughout the first weeks of L.V.'s life, he had red and swollen eyes with yellow drainage. Pet'rs' Ex. 3 at 5. He was ultimately diagnosed with acute nasolacrimal stenosis,[4] and then subsequently diagnosed with gastro-esophageal reflux [5] during his first well-child appointment on March 31, 2005. *Id*. at 5, 25.

At L.V.'s second well-child appointment on May 12, 2005, he was determined to be developing appropriately for his age, and received: (a) Diphtheria, Tetanus, and acellular Pertussis ("DTaP") vaccine; (b) haemophilus influenza type B ("Hib") vaccine; (c) inactivated polio vaccine ("IPV"); and (d) pneumococcal conjugate vaccine ("PCV"). Pet'rs' Ex. 3 at 113-14. A month later, L.V. was diagnosed with onychia.[6] *Id.* at 37-41.

On July 22, 2005, L.V. had his third well-child visit, at which time his pediatrician, Dr. Sharon Corcoran, evaluated him as developing appropriately for his age. Pet'rs' Ex. 3 at 50-51.

[3] The medical records in this case are particularly voluminous, and include many records pertaining to efforts to treat L.V.'s autism (and possible causes of it) post-vaccination that only bear tangentially on the issues to be resolved in this entitlement proceeding. Although I have reviewed the entire record, 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.

[4] Acute nasolacrimal stenosis is the short term narrowing of the tear duct. *Dorland's Illustrated Medical Dictionary* (32d ed. 2012) at 24, 1233, 1769 [hereinafter *Dorland's*]. *See also Nasolacrimal Duct Obstruction*, AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS (July 2014), http://www.aapos.org/terms/conditions/72.

[5] Gastro-esophageal reflux is defined as the "reflux of the stomach and duodenal contents into the esophagus, which sometimes occurs normally, particularly in the distended stomach" after meals, or "as a chronic pathological condition that leads to the conditions known as *gastroesophageal reflux disease* and *reflux esophagitis*." *Dorland's* at 1616 (emphasis in original).

[6] Onychia refers to the "inflammation of the matrix of the nail resulting in shedding of the nail." *Dorland's* at 1321.

L.V. again received the DTaP, Hib, IPV, and PCV vaccines. *Id.* at 113, 114. On August 15, 2005, L.V. developed cold symptoms including a cough, as well as a possible toe infection. *Id.* at 54, 56, 59. L.V. was prescribed augmentin[7] for his toe infection and his parents subsequently reported that he experienced vomiting and an upset stomach. *Id.* at 61, 63.

On September 16, 2005, L.V. had his fourth well-child visit, and once again Dr. Corcoran evaluated L.V. as developing appropriately for his age. Pet'rs' Ex. 3 at 66. At this time L.V. received the DTaP, IPV, and PCV vaccines, after which he developed a localized rash. *Id.* at 69, 113, 114. Months later, on December 16, 2005, L.V. was again evaluated by Dr. Corcoran as developing appropriately for his age. *Id.* at 77.

As L.V. approached his first birthday, there remained no obvious signs of developmental problems. In February of 2006, L.V. was taken to the pediatrician because he was experiencing diarrhea, and was diagnosed with gastroenteritis.[8] Pet'rs' Ex. 3 at 93. On March 16, 2006, Dr. Corcoran determined that L.V. was still developing appropriately for his age, and at that time he received the hepatitis B; measles, mumps, and rubella ("MMR"); and varicella vaccines. *Id.* at 96, 98, 114. In March of 2006, L.V. was diagnosed with both peanut butter and blueberry allergies. *Id.* at 100, 102, 110. On July 10, 2006, L.V. was again evaluated as overall developing appropriately for his age and received the DTaP and PCV vaccines. *Id.* at 112, 194. L.V. was taken back to Dr. Corcoran's office on August 7, 2006, where he was diagnosed with "other acute sinusitis" and prescribed amoxicillin.[9] Pet'rs' Ex. 3 at 115, 117. In September of 2006, the Vs called Dr. Corcoran to report that L.V. was experiencing diarrhea, and Dr. Corcoran prescribed home management. *Id*. at 119.

On September 8, 2006, L.V. visited the pediatrician for a 17-18 month well-child appointment. At this visit, L.V. was assessed as having normal growth and development (including motor skills such as use of a cup and spoon), and received the hepatitis A vaccine. Pet'rs' Ex. 3 at 123-24, 194. Later that same month, the Vs also brought L.V. to Allergy and Asthma Specialists, P.C. in Flourtown, Pennsylvania, because L.V. had developed a large hive after eating blueberry yogurt and pancakes. Pet'rs' Ex. 7 at 39-40.

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[7] Augmentin is "the trademark for combination preparations of amoxicillin and clavulanate potassium." *Dorland's* at 179.

[8] Gastroenteritis refers to the "inflammation of the lining of the stomach and intestines." *Dorland's* at 764.

[9] Amoxicillin is a "semisynthetic derivative of ampicillin effective against a broad spectrum of gram-positive and gram-negative bacteria." *Dorland's* at 65.

B. Flu Vaccine Administration and Subsequent Developmental Regression.

L.V. received the first dose of flu vaccine on November 8, 2006 (at approximately 20 months of age), and the second on December 8, 2006 (at approximately 21 months of age).[10] Pet'rs' Ex. 3 at 125, 128-29. Records from these two pediatric visits say nothing about developmental problems, and there are no records from the intervening period between visits.

Three days after L.V. received the second flu vaccine dose, on December 11, 2006, Mrs. V phoned the pediatrician's office to report that L.V. was experiencing serious constipation "for a while," and had not had a bowel movement since December 9th. Pet'rs' Ex. 3 at 132. She reported no other problems, however. An office appointment was set for December 13, 2006. *Id.*

At the December 13th visit, Mrs. V again identified only constipation as the reason for the appointment. Pet'rs' Ex. 3 at 134-35. Thus, the medical records explicitly state that L.V. had not been "going regularly for 1-2 months" despite alteration of his diet. *Id*. In addition to the constipation, L.V. also now presented with left otitis media,[11] although the records do not state that he had a fever, and in fact state he displayed no acute distress. *Id*. at 135. Significantly, for the first time the pediatric records reflect a concern with "speech delay," although no details are given as to the source of this concern. *Id.* L.V. was prescribed miralax for constipation and amoxicillin for the ear infection, with the recommendation that any pain/fever that later resulted be treated with an over-the-counter medication such as Tylenol or Motrin. *Id*. Mrs. V was instructed to return to the pediatrician if symptoms did not improve in three days. *Id*. The speech delay was to be evaluated through a hearing screen once the ear infection resolved, but the record also notes that Mrs. V was supplied with a phone number for early intervention services in Montgomery County, Pennsylvania. *Id.* at 135, 137.

Over a week passed without any further contact with L.V.'s pediatrician. Then, on December 22, 2006, Mrs. V called Dr. Corcoran's office to report that L.V. (who had been on antibiotics to treat the ear infection for nine days) had now developed a fever of 102 degrees (which later that same day rose to 104 degrees). Pet'rs' Ex. 3 at 138-40. L.V.'s treaters prescribed

[10] The flu vaccine is an "inactivated trivalent virus vaccine, containing two influenza A virus strains and one influenza B virus strain, usually prepared from virus subunits." *Dorland's* at 2016. "The composition of the vaccine is changed each year in response to antigenic shifts and changes in prevalence of influenza virus strains." *Id*. L.V. received the trivalent influenza vaccination, including one type B and two type A strains. Am. Pet. at 1 (ECF No. 27); *see also* 2006-2007 Influenza (Flu) Season, CENTERS FOR DISEASE CONTROL AND PREVENTION (July 8, 2009), http://www.cdc.gov/flu/pastseasons/0607season.htm.

[11] Acute suppurative otitis media refers to a short course inflammation of the ear with a discharge of pus. *Dorland's* at 24, 1351.

augmentin and recommended an in-office visit if L.V.'s symptoms did not improve in the next few days. *Id.* at 138.

L.V.'s follow-up pediatric visit occurred on December 26, 2006. Pet'rs' Ex. 3 at 142-47. At this point, the Vs reported to L.V.'s treaters that he was suffering from rashes on his face, shoulders, back, and diaper area that had first become evident on December 23rd, along with a cough and runny nose. *Id.* at 144. The records make no mention, however, of an ongoing fever (beyond reference to the fever that the Vs reported on December 22nd), and indicate that L.V. displayed no particular distress. Dr. Corcoran diagnosed L.V. as suffering from an augmentin allergy (based upon the circumstantial link between the time that medication was started and the rash development), and he was prescribed omnicef as a substitute for augmentin. *Id.* at 142, 144.

Before their first visit to the pediatrician in 2007, the Vs obtained an initial early intervention assessment from Montgomery County's provider on January 17, 2007, after requesting it on January 10th. *See generally* Pet'rs' Ex. 13 at 1-11 and Ex. 30 at 475. The written report generated from this initial assessment (based on observation of L.V. along with parental reports) placed L.V. at eleven months for cognitive development, ten months for communication development, six months for social development, and sixteen months for fine motor/physical development. Pet'rs' Ex. 13 at 5-6. The report contains references to L.V. having lost language or expressive abilities, but notes that "he lost these abilities around 18 months." *Id.* at 8. In addition, other developmental problems (such as not responding to his name, or making eye contact) are noted as uncommon occurrences, rather than behaviors that abruptly ceased or regressed. *See, e.g.*, *Id.* at 5 (L.V. "did not respond to his name today. Parents report that he will respond to his name 20% of the time (at best)").

L.V.'s next pediatric visit was on January 18, 2007. Pet'rs' Ex. 3 at 148-49. Although L.V. returned to Dr. Corcoran in part for a follow-up visit regarding his ear infection, the Vs also made it clear that they wished to discuss "developmental issues." *Id.* at 149. Specifically, the medical records from that visit note the Vs' statements that L.V. had "lost some of his language and does not make a lot of eye contact." *Id*. at 149. The January 18th records do not indicate when the lost language began or was first observed – nor do they make any reference to the flu vaccine or L.V.'s subsequent ear infection, brief fever, or rash as having any role in such developmental matters. However, these records substantiate that the Vs had already initiated the process for obtaining an early intervention assessment, as noted above. *Id.* at 149.

Dr. James Coplan, M.D., of Neurodevelopmental Pediatrics of the Main Line, P.C. in Rosemont, Pennsylvania thereafter (upon referral by Dr. Corcoran) performed another early evaluation assessment, completing his write-up of the assessment on January 23, 2007. *See generally* Pet'rs' Ex. 5 at 3-7. The assessment was based on both a physical examination and a medical and personal history provided by the Vs (including the January 17th early assessment

report). Dr. Coplan's conclusions were discouraging: he diagnosed L.V. with autism or autism spectrum disorder ("ASD").[12] *Id.* at 4, 6. Consistent with the prior assessment performed by Montgomery County, Dr. Coplan noted regressive developmental issues, as well as developmental plateaus or behaviors that had not properly manifested. L.V.'s use and acquisition of words is said to have "faded and disappeared" around 18-20 months (*id.* at 4), but L.V. never "reliably" said "mama" or "dada" at all (a ten-month developmental milestone), while other behaviors (such as fine motor skills in self-feeding) that should have begun earlier were only recently manifesting (such as scoop-feeding with a spoon, which the Vs identified to Dr. Coplan as having begun only "within the past week or two"). *Id.* at 1, 3-4.[13] L.V. was scored at 40 on the Childhood Autism Rating Scale[14] (with 30 being the cutoff for autism). *Id.* at 6.

Dr. Coplan's assessment included some discussion of the course of L.V.'s developmental problems. He thus noted that the developmental and skills "deterioration" in a child's second year, as evidenced by L.V.'s history, occurs in 20 percent of autistic children. Pet'rs' Ex. 5 at 6. However, Dr. Coplan also proposed that despite the "striking history of developmental deterioration" at 18 months provided by the Vs' personal recollections, it was not entirely clear that L.V. was truly regressing developmentally, given other information provided by the Vs about L.V.'s earlier developmental abnormalities (such as his failure to "acquire appropriate use of 'mama' and 'dada'). *Id.* at 6. Dr. Coplan also indicated that it was unlikely the immunizations that L.V. had received played any role in his development of autism (and this record does not contain any statement from the Vs linking L.V.'s alleged regression and his receipt of the flu vaccine in November and December of 2006). *Id.* at 6.

The Vs later obtained a child development evaluation from Dr. Hillary Kruger, M.D., at Children's Hospital of Philadelphia ("CHOP"). *See generally* Pet'rs' Ex. 6. In her initial pediatric evaluation, dated May 21, 2007, Dr. Kruger concurred with the autism diagnosis proposed earlier that year by Dr. Coplan. *Id.* at 5. Her written report also references previous records from 2007 in which the Vs had stated to treaters that they noticed L.V.'s regression when he was 18 to 19 months old. *Id.* at 1.

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[12] Section IV(A) of this decision contains a discussion of ASDs generally.

[13] As discussed below, however, Petitioners contest the accuracy of Dr. Coplan's assessment that L.V.'s spoon usage was delayed, pointing to a contrary, earlier pediatric record suggesting normal development. *See* Pet'rs' Ex. 3 at 122.

[14] The Childhood Autism Rating Scale "helps to identify children with autism and determines symptom severity through quantifiable ratings based on direct observation." *Childhood Autism Rate Scale, Second Edition (CARS-2)*, WPS, http://www.wpspublish.com/store/p/2696/childhood-autism-rating-scale-second-edition-cars-2 (last visited Feb. 3, 2016).

C. Dating the Onset of L.V.'s Regression.

In this action, Petitioners have alleged that L.V. experienced a dramatic developmental regression after he received the second flu vaccine. However, as the medical records contemporaneous with L.V.'s alleged regression consistently reveal, the Vs repeatedly reported to doctors that L.V.'s regression began no later than when he was 18 to 19 months old.

As noted above, the contemporaneous records from January of 2007 (when Dr. Coplan evaluated L.V. at 22 months of age) reveal that the Vs informed treaters such as Drs. Coplan and Kruger that L.V.'s developmental problems and/or regression had been evident to them since L.V. was 18 months old, or around September of 2006. Pet'rs' Ex. 5 at 3. This reported onset is repeated numerous other times in the subsequent medical record. Thus, Mrs. V informed Dr. James A. Neubrander in September of 2007 (when L.V. was almost two and a half years old) that at 19 months she noticed L.V. had lost the few words he had, lost social interest, and appeared withdrawn and irritable, and at around 20 months, L.V. lost eye contact, began constantly jumping, became increasingly irritable, and began making only a few sounds with vibrations. Pet'rs' Ex. 8 at 4. Dr. Bryan Jepson's 2008 notes corroborate the same timeframe, reporting that according to the Vs "[t]here was a regression from normal development around age 12 months in hindsight: more noticeable around 18 months" including "arm flapping, loss of contact, less socially interactive, [and] loss of his few words." Pet'rs' Ex. 10 at 5.

There are many other similar examples from the medical record. *See, e.g.*, Pet'rs' Ex. 7 at 29-30 (January 31, 2007 visit to CHOP for genetic testing); Pet'rs' Ex. 10 at 78 (April 15, 2007 visit at Thoughtful House with Dr. Jepson); Pet'rs' Ex. 6 at 1 (May 21, 2007 visit with Dr. Kruger); Pet'rs' Ex. 9 at 6 (June 14, 2007 visit with Dr. Krigsman); Pet'rs' Ex. 8 at 3 (September 27, 2007 visit with Dr. Neubrander); Pet'rs' Ex. 8 at 32 (September 29, 2007 visit with Dr. Neubrander).

D. The Vs' Attempts to Explain L.V.'s ASD.

After L.V.'s initial ASD diagnosis in January of 2007, the Vs (whom the record underscores were extremely dutiful in caring for their son) explored possible explanations for L.V.'s autism, as well as treatments that would be effective under the circumstances. Eventually they became very interested in determining whether L.V.'s purported post-vaccine regression had something to do with an underlying disorder involving dysfunction (if not disease) in his mitochondria and their efficiency in producing energy.

To that end, the Vs consulted with a variety of autism specialists, some of whom were themselves exploring the links between autism and mitochondrial diseases. In May of 2007, L.V. saw Dr. Corcoran and Dr. Hilary Kruger, a developmental pediatrician, both at CHOP, who determined after genetic testing and evaluation that L.V. had no clinically significant genetic

abnormalities[15] and had normal weight gain and growth. Pet'rs' Ex. 6 at 1-5; Pet'rs' Ex. 7 at 36-37.[16] L.V.'s ASD diagnosis was at that time confirmed as well. *Id.*

The Petitioners next brought L.V. to Texas specifically in search of a Defeat Autism Now ("DAN")[17] doctor, and found Dr. Arthur Krigsman at Thoughtful House, in Austin, Texas. Tr. at 92. The Thoughtful House is associated with the DAN movement. Pet'rs' Ex. 9 at 1. Dr. Krigsman referred L.V. for an endoscopy and colonoscopy, which were performed by Mount Sinai on June 14, 2007. *Id*. His results showed mild lymphonodular hyperplasia. *Id*. L.V. was also diagnosed with duodenal ulcers, gastritis, and suspected esophagitis. *Id*. at 2. L.V. also saw Dr. Jepson (a member of Thoughtful House) for the first time on June 19, 2007. Pet'rs' Ex. 10 at 7. Dr. Jepson continued treating L.V. through the end of 2008, prescribing various medications and supplements and at-home behavioral intervention therapy to treat L.V.'s autism. *Id*. at 1.

At the recommendation of Dr. Krigsman and other Thoughtful House practitioners, the Vs traveled to New Jersey to bring L.V. to see Dr. Neubrander, another noted DAN doctor, who L.V. first saw on September 29, 2007. Pet'rs' Ex. 8 at 1-3. Following a physical exam performed that same day, Dr. Neubrander confirmed L.V.'s autism diagnosis, and also diagnosed him with "gastroenteritis associated with autistic spectrum disorders" and nutritional deficits. *Id*. at 36-37.[18]

The Vs eventually obtained treatment from Dr. Richard Frye, beginning in August of 2008, who at the time was a physician at the Child and Adolescent Neurology Clinic at the University of Texas Health Science Center in Houston, Texas. Pet'rs' Ex. 8 at 2. Petitioners learned of Dr. Frye from Dr. Krigsman, and it was Dr. Frye who first proposed to them that L.V. might have some

[15] L.V. was found to have a duplication of 1q44, which he appears to have inherited from his father, but the lab interpretation noted that this may represent a normal population variant. Pet'rs' Ex. 7 at 1.

[16] During this time, the Vs continued seeking assessments of L.V. to better his daily life. In April of 2007, the Vs took L.V. for an occupational therapy assessment after which he received ongoing occupational therapy through at least July of 2007, when the records stop. *See generally*, Pet'rs' Ex. 15. They also brought L.V. for an applied behavior analysis/verbal behavior evaluation in May of 2007. *See generally* Pet'rs' Ex. 16. In July of 2007, L.V. had a communication evaluation. *See generally* Pet'rs' Ex. 17. Finally, in November of 2007, L.V. underwent a Behavior Language Assessment. *See generally* Pet'rs' Ex. 18, 19.

[17] DAN is composed of doctors and medical professionals who believe, among other things, that autism can 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).

[18] The Vs later brought L.V. back to Pennsylvania and saw Dr. Coplan again in the winter of 2008. Dr. Coplan maintained his diagnosis of autism with unclear underlying cause; he also recommended some additional metabolic testing, but noted that testing performed for methylene tetrahydrofolate reductase did not indicate any abnormality. Pet'rs' Ex. 5 at 11-13.

kind of mitochondrial disease that had played a role in his ASD. Tr. at 93-94. The Vs traveled back to Texas in order to obtain Dr. Frye's services.

Dr. Frye performed testing to evaluate whether in fact L.V. displayed any of the clinical indicia necessary for a mitochondrial disease diagnosis. At L.V.'s first visit with Dr. Frye on August 1, 2008, extensive blood work was performed. Pet'rs' Ex. 11 at 3. Then, on December 3, 2008, Dr. Frye had Quest Diagnostics, Inc. perform an amino acid analysis and a comprehensive metabolic panel, intended to clarify what type of mitochondrial disorder L.V. had, if any. *Id.* at 17-22.

Initial test results did not suggest the existence of a specific or inherited metabolic defect, and returned an essentially normal acylcarnitine profile.[19] Pet'rs' Ex. 11 at 2, 6, 18, 20. But the same lab results also showed elevated lactate (with values of 18 and 23 on a normal range of 4-16) (Pet'rs' Ex. 21 at 29), urinary tricarboxylic acid[20] excretion (indicated by high levels of ammonia, of which L.V. had a value of 83 when normal is equal to or below 47) (*id.* at 12), and the presence of ethylmalonic aciduria. *Id.* at 13. [21]

In 2009, L.V. underwent additional testing at Dr. Frye's direction, through the Mitochondrial Diagnostic Laboratory of the Medical Genetics Laboratories of the Baylor College of Medicine ("BCM") in Houston, Texas. *See generally* Pet'rs' Ex. 34. There, specialists performed a MitoMet oligo aCGH analysis[22] that came back negative, showing no abnormalities. Pet'rs' Ex. 34 at 4. A year later, on September 9, 2010, the Urinary Creatine and Guanidinoacetate results from BCM, Biochemical Genetics Lab suggested the possibility of a creatine transporter deficiency,[23] but further clinical correlation was needed. Pet'rs' Ex. 26 at 37. Shortly thereafter,

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[19] Acylcarnitine profile analysis "is performed for the biochemical screening of disorders of fatty acid oxidation and organic acid metabolism." P. Rinaldo, et al., *Acylcarnitine profile analysis*, 10 GENETICS IN MEDICINE 151 (2008), http://www nature.com/gim/journal/v10/n2/full/gim200822a.html (last visited Feb. 11, 2016).

[20] The Krebs Cycle, or the tricarboxylic acid cycle, is "the final common pathway for the oxidation to CO_2 of fuel molecules, most of which enter the cycle as acetyl coenzyme A." The cycle occurs "in the mitochondria and generates ATP by providing electrons to the electron transport chain." *Dorland's* at 454.

[21] Ethylmalonic aciduria is a genetically heterogeneous disorder due to deficiencies in the electron transport system, characterized by the accumulation and excretion of acids normally oxidized by mitochondria. *Dorland's* at 652, 791. The presence of high ethylmalonic acid is a biomarker for mitochondrial disease and/or dysfunction. Tr. at 449-50; 560-62.

[22] The MitoMet oligo aCGH analysis is used to detect some genetic deletions or duplications involved in mitochondrial and metabolic related diseases. *Medical Genetics Test: MitoMet®Plus aCGH Analysis*, BAYLOR MIRACA GENETICS LABORATORIES, https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=2000 (last visited Feb. 11, 2016).

[23] Creatine transport deficiency is a genetic syndrome caused by mutations in the SLC6A8 gene on the X chromosome. Pet'rs' Ex. 26 at 6.

on September 16, 2010, a Magnetic Resonance Spectroscopy ("MRS")[24] test produced results indicating that L.V.'s major metabolites were normal for his age, and there was evidence of a normal creatine peak[25] as well. *Id.* at 40. Not long thereafter, on October 14, 2010, the Mitochondrial Diagnostic Lab at BCM preformed a creatine transporter 1 sequencing test that detected no known deleterious mutations in the CRTR.[26] Pet'rs' Ex. 34 at 8.

During the time of this testing under Dr. Frye's direction, the Vs brought L.V. back to CHOP. Pet'rs' Ex. 36 at 18. Metabolic studies of L.V. performed on August 12, 2010, "were essentially normal and were not suggestive of metabolic or mitochondrial dysfunction." *Id.*; Pet'rs' Ex. 26, Part 2 at 1-9. During their September 2, 2010, visit, the doctors confirmed that interpretation. Pet'rs' Ex. 36 at 18.

By the fall of 2010, the Vs sought the opinion of another specialist with views similar to Dr. Frye's regarding the possible metabolic causes of autism, Dr. Richard Kelley at the Kennedy Krieger Institute in Baltimore, Maryland. Dr. Frye had recommended in August of 2010 that Petitioners speak with Dr. Kelley (Pet'rs' Ex. 33 at 30), and (in written communication introducing the Vs to him) set forth the opinion that L.V. had a "mitochondrial complex deficiency." Pet'rs' Ex. 26 at 4. Dr. Kelley and his assistants subsequently reviewed L.V.'s lab work. *Id.* at 32-33. After review of the relevant results and L.V.'s history, however, Dr. Kelley expressed the belief that there were "no metabolic abnormalities," and thus nothing consistent with mitochondrial dysfunction (although he acknowledged that L.V.'s condition could be consistent with an encephalitis). *Id.*

Despite such inconclusive results, the Vs nevertheless pursued further attempts to identify the source of L.V.'s ASD. To that end, on January 21, 2011, L.V. underwent a muscle biopsy, performed to measure lactic acid[27] levels (with the tested sample taken from L.V.'s right lateral

[24] MRS is "a noninvasive diagnostic test for measuring biochemical changes in the brain, especially the presence of tumor." *Magnetic Resonance (MR) Spectroscopy*, Mar. 2010, MAYFIELD BRAIN & SPINE, http://www mayfieldclinic.com/PE-MRspectroscopy.htm (last visited Feb. 11, 2016). "Spectroscopy is a series of tests that are added to the MRI scan of your brain or spine to measure the chemical metabolism of a suspected tumor." *Id.*

[25] Creatine is "an amino acid formed by methylation of guanidinoacetic acid, found in vertebrate tissues, particularly in muscle." *Dorland's* at 429.

[26] The CRTR "is in a sodium chloride dependent transporter 1 that belongs to the solute carrier family 6 member 8 (SLC6A8)." Pet'rs' Ex. 34 at 8. "In patients with CRTR deficiency, the urinary creatine excretion relative to the creatinine excretion is elevated, and the creatine/creatinine ratio can be used as a first biochemical diagnostic marker for CRTR deficiency." *Id.*

[27] Lactic acid is "a metabolic intermediate involved in many biochemical processes; it is the end product of glycolysis, which provides energy aerobically in the heart for energy production or can be converted back to glucose." *Dorland's* at 997. While elevated lactic acid in the blood is not specific for a diagnosis of mitochondrial disease (Tr. at 133-34), it has previously been used as a measurement of autism in children. *Dorland's* at 571.

thigh muscle), at BCM. Pet'rs' Ex. 23 at 3. The results showed: "[f]iber type 1 predominance, moderate" and "[m]ildly increased oxidative enzyme reaction (COX), and increased mitochondria by electron microscopy." *Id*. Nevertheless, L.V.'s muscle biopsy was interpreted by the performing neuropathologist to show "no specific pathologic findings," and he recommended further enzyme tests aimed at analyzing the functioning of the electron transport chain ["ETC"][28] in L.V.'s mitochondria, or additional attempts to measure mitochondrial DNA. Pet'rs' Ex. 33 at 121.

Such additional testing was performed at Dr. Frye's direction in late January of 2011, but detected no deficiencies in L.V.'s mitochondrial ETC enzymes. Pet'rs' Ex. 23 at 1-3. However, the mitochondrial DNA content analysis performed at BCM on February 7, 2011, showed that L.V.'s muscle contains approximately 189% of the mean value of the age and tissue-matched controls, suggesting a compensatory amplification of mitochondrial DNA due to some other kind of mitochondrial dysfunction. Pet'rs' Ex. 34 at 16. A follow-up ETC test performed at BCM on February 22, 2011, once again did not detect any deficiencies. *Id.* at 9.

In spite of such generally inconclusive data, on August 4, 2011, Dr. Frye diagnosed L.V. (who was at that time six years old) with a mitochondrial disorder. Pet'rs' Ex. 72, Part 2 at 25-26. He did so by applying criteria set forth in an article written by Morava, entitled *Mitochondrial Disease Criteria, Diagnostic Applications in Children* (the "Morava criteria"). Pet'rs' Ex. 41, Ref. 25 at 31 (E. Morava, et al., *Mitochondrial disease criteria: Diagnostic applications in children*, 67 NEUROLOGY 1823 (Nov. 2006) [hereinafter Morava]). As discussed in greater detail below, Morava set forth diagnostic guidelines 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. Pet'rs' Ex. 24 at 1; Tr. at 120-21, 442-44.

In a "to whom it may concern" letter dated February 29, 2012, Dr. Frye identified the specific grounds for his conclusion that L.V. suffered from a "definite" mitochondrial disease (based on application of the Morava criteria). *See generally* Pet'rs' Ex. 24 at 1-3. In his opinion, L.V. exhibited three clinical signs consistent with a mitochondrial disorder, including: (i) exercise intolerance, (ii) history of regression in skills, and (iii) gastrointestinal abnormalities. *Id.* at 1. Dr. Frye then listed three metabolic indicators (based on previous bloodwork) he found significant, including: (i) elevated lactate,[29] (ii) urinary tricarboxylic acid excretion, and (iii) ethylmalonic aciduria. *Id*. Dr. Frye also noted that L.V. had abnormal mitochondrial morphology[30] as viewed

[28] An electron transport chain is embedded within the inner mitochondrial membrane, and makes the same chemical reduction of oxygen to water. Tr. at 428. "The oxidation of the carbon to carbon dioxide regenerate ATP as opposed to an explosive force" and then the ATP is used by the cell to function, including muscle contraction, allowing the eyes to see, the heart to beat, the ears to hear, etc. *Id*. at 428-29.

[29] Lactate is the anionic form of lactic acid. *Dorland's* at 997.

[30] Mitochondrial morphology refers to the form and structure of the mitochondria. *Dorland's* at 1169, 1181.

via electron microscopy ("EM").[31] *Id.* These factors were enough to score a "9" in Dr. Frye's application of the Morava criteria, resulting in the conclusion that L.V. definitely had a mitochondrial disease. Dr. Frye also suggested, without elaboration, that the ETC test results and muscle biopsy results supported his conclusion, while admitting at the same time that the genetic evidence supporting his diagnosis was lacking. *Id.*

II. PROCEDURAL HISTORY

As stated above, the Vs filed this petition in 2008. On May 6, 2009, Respondent filed a statement expressing no objection to the jurisdiction and appropriateness of Petitioners proceeding within the Omnibus Autism Proceeding ("OAP").[32] However, after the relevant test cases in the OAP were litigated, and their causation theories rejected, the Vs elected to remain in the Vaccine Program, filing an amended petition on April 9, 2012, that explained how their revised theory of vaccine causation differed from the decided test cases. ECF No. 27.

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[31] Electron microscopy involves the use of a microscope "in which an electron beam, instead of light, forms an image for viewing, allowing much greater magnification and resolution." *Dorland's* at 1162.

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

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

The first theory was rejected in three test case decisions, all of which were subsequently affirmed. *See generally Cedillo v. Sec'y of Health & Human Servs.*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for review den'd*, 89 Fed. Cl. 158 (2009), *aff'd*, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec'y of Health & Human Servs.*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *mot. for review den'd*, 88 Fed. Cl. 473 (2009), *aff'd*, 605 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec'y of Health & Human Servs.*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *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 eleven lengthy decisions by special masters, the judges of the U.S. Court of Federal Claims, and the panels of the U.S. Court of Appeals for the Federal Circuit, unanimously rejected petitioners' claims. These decisions found no persuasive evidence that the MMR vaccine or thimerosal-containing vaccines caused autism. The OAP proceedings concluded in 2010.

After filing a statement of completion on September 25, 2012, Petitioners offered the expert report of Dr. Frances Kendall on August 20, 2013. ECF No. 64. On February 19, 2014, Respondent filed a Rule 4(c) Report, contending that the record failed to establish by preponderant evidence the causal connection between the flu vaccine and L.V.'s subsequent conditions, and disputing the reliability of Petitioners' medical theory. ECF No. 71. In response, Respondent filed an expert report from Dr. Bruce Cohen. ECF No. 72. The Vs then elected to file a supplemental expert report from Dr. Yuval Shafrir on December 30, 2014. ECF No. 95. With records gathering and the filing of relevant evidence and expert reports complete, a two-day entitlement hearing was set for April of 2015. (Petitioners later moved to file out of time a second supplemental expert report from Dr. Shafrir on March 17, 2015 (ECF No. 129), and I permitted them to do so.)

On January 4, 2015, Petitioners filed a second amended petition that presented facts and allegations relevant to Petitioners' claim for compensation.[33] ECF No. 105. The next day, Petitioners filed: (i) their Prehearing Submissions (ECF No. 111); and (ii) a motion to compel Respondent's admission of Petitioners' medical theory, alleging that Respondent had conceded Petitioners' theory in the case *Poling v. Sec'y of Health & Human Servs.*, No. 02-1466v, 2008 WL 1883059 (Fed. Cl. Spec. Mstr. Apr. 10, 2008) through Respondent's Rule 4(c) Report in that case. ECF No. 112. After considering each side's arguments, I denied Petitioners' Motion for Judicial Estoppel in my March 6, 2015, Order. ECF No. 124.[34] In the meantime, Respondent filed her prehearing submissions on February 24, 2015. ECF No. 119. Petitioners then filed their prehearing submissions reply on March 9, 2015. ECF No. 127.

On April 13-14, 2015, a two-day entitlement hearing was held. During the hearing, I heard testimony from Mrs. V; Petitioners' experts Drs. Kendall and Shafrir; and Respondent's expert Dr. Cohen. After requesting two extensions of time (ECF Nos. 147 and 152) both of which I granted, Petitioners filed their post-hearing brief on July 13, 2015. ECF No. 155. In response, Respondent then filed her post-hearing brief on September 14, 2015. ECF No. 157. Petitioners replied to Respondent's argument on October 14, 2015.

III. TESTIMONY PRESENTED AT HEARING

A. Mrs. V

E.V., L.V.'s mother, was the only non-expert witness who testified at the entitlement hearing. *See generally* Tr. at 7-103. Her testimony provided some context about L.V.'s overall development – and also sought to rebut the notion, reflected in the medical records, that the Vs

[33] On July 6, 2015, the Parties filed a stipulation for interim fees and costs (ECF No. 148), and I entered a decision awarding the stipulated amount on July 7, 2015. ECF No. 150.

[34] Petitioners filed a Motion for Reconsideration of that Order on April 4, 2015 (ECF No. 137) which I subsequently denied by Order dated April 10, 2015. ECF No. 148.

were aware of signs of L.V.'s regression before he received the flu vaccines in November and December 2006. In order to do so, she frequently attempted to diminish the weight to be given statements in the medical record reporting earlier onset.

Thus, Mrs. V repeatedly stressed that the first time she or her husband had observed developmental issues with L.V. was in mid-December of 2006, after he received the second dose of flu vaccine. *Compare* Tr. at 29, 36, 40 *with* Tr. at 56, 58. Some photographs of L.V. were offered to bulwark her assertions that L.V.'s pre-vaccination development was completely normal. *Id*. at 54-74.[35] Yet she also admitted that she had witnessed some "subtle issues" pertaining to L.V.'s development a month to two months before the second flu vaccine was administered. *Id*. at 54, 88.

More significantly, Mrs. V was unable to deny the many instances from the contemporaneous medical records in 2007 in which she and/or her husband reported to treaters evaluating L.V.'s autism that L.V. first displayed such symptoms by the time he was 18 months old. For example, on cross-examination, Respondent pointed out that the excel sheet prepared by Mrs. V documenting L.V.'s issues and presented to Dr. Neubrander at L.V.'s September 29, 2007, visit reported that at 19 months L.V. "lost a few words he had, lost social interest, seemed withdrawn, irritable." Tr. at 87-88; Pet'rs' Ex. 8 at 4. This is in apparent contradiction to Mrs. V's testimony (nearly nine years after the events in question) and her affidavit (prepared nearly three years after the vaccination), both of which maintain that L.V.'s regression manifested no sooner than 21 months, or after his receipt of the flu vaccine in December 2006. *Compare* Tr. at 29, 36, 40 *with* Tr. at 56, 58. Mrs. V had also prepared a narrative for Dr. Krigsman for L.V.'s June 2007, visit, which is similarly inconsistent with her testimony and affidavit. *Id*. at 90; Pet'rs' Ex 9 at 6 (reporting that L.V. "did always seem to be more difficult than other children" and that he "began flapping his arms as early as 12 to 18 months").

To the extent Mrs. V admitted that she had made such statements about the actual onset of L.V.'s ASD-related symptoms, she attempted to downplay their significance, suggesting that she and her husband had not considered L.V.'s earlier symptoms to be alarming enough to merit a medical response. Tr. at 63. This line of reasoning – that L.V.'s "real" regression began only after the second flu vaccine administration, and that any earlier signs of developmental problems were too inconclusive to meaningfully relate to the later, agreed-upon developmental difficulties L.V. experienced – was a general theme that Petitioners and their experts came back to during the

[35] The Vs provided an array of photographs, and three videos, in an attempt to demonstrate visually that L.V. had experienced a significant change in behavior and affect following his receipt of the second dose of flu vaccine in December of 2006. *See generally* Pet'rs' Ex. 43-65, 74-79. Neither of Petitioners' experts commented on this evidence at length. While these photographs do show L.V. demonstrating a variety of emotions and engaging in multiple social interactions, and generally support the conclusion that L.V. has been well-loved and cared for, I do not find this evidence probative in establishing the onset of L.V.'s purported regression. I could not draw useful conclusions or inferences about L.V.'s capacity or developmental state at the time each photograph was taken simply by looking at them, and testimony Mrs. V offered to explain them did not increase their evidentiary value.

hearing multiple times. *See, e.g.*, *id*. at 86, 93, 152, 179-80.

B. Petitioners' Experts[36]

1. Dr. Frances Kendall

Dr. Kendall offered an expert report and testimony at the entitlement hearing in support of Petitioners' theory that L.V. likely had an underlying, preexisting mitochondrial disease that was exacerbated by receipt of the flu vaccine, thereby precipitating L.V.'s autism.

Dr. Kendall graduated from UMDNJ-New Jersey Medical School in 1987 after which she completed her residency in pediatrics at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania. Pet'rs' Ex. 42 at 1; Tr. at 106. From 1990 to 1993 she completed two fellowships in genetics and metabolism at Children's Hospital and Harvard Medical School and Tufts University and is licensed by the American Board of Medical Genetics. Pet'rs' Ex. 42 at 1; Tr. at 106. She has worked and taught across the country in genetics and metabolism, including as Director of the Mitochondrial Disorders Program at the Children's Hospital of Boston, and written extensively, including her own reports and reviews of others, on issues of mitochondrial energy production and the errors of metabolism. Pet'rs' Ex. 42 at 6-8; Tr. at 106, 108-09. She is presently board-certified in biochemical genetics, and was previously board-certified in pediatrics. Tr. at 111. Dr. Kendall currently treats patients from all over the world "for evaluation of and management of mitochondrial disease" and estimates that since 2009 she has seen about a thousand patients, most of whom she continues to treat. *Id*. at 105.

Dr. Kendall's expertise thus lies in the specific field of mitochondrial disorders. Tr. at 104. She did not, however, claim expertise in autism or in immunology. *Id.* at 233-34. In preparing her expert opinion, Dr. Kendall reviewed the contemporaneous pediatric records, including L.V.'s various evaluations discussed above, although she admitted that certain records relevant to Dr. Frye's analysis of L.V. were not provided to her at the time of her report's preparation in July of

[36] Petitioners' two experts offered in total 71 individual articles or pieces of medical literature (in addition to the 101 articles also filed by Petitioners but not directly relied upon by their experts). Although I have reviewed all such submitted evidence, I do not herein discuss, or include a summarization of, each individual article offered in this case. *La Londe v. Sec'y of Health & Human Servs*., 110 Fed. Cl. 184, 209 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014) (on appeal, it is presumed that special master reviewed all literature submitted in support of vaccine claim); *Hennessey v. Sec'y of Health & Human Servs.,* 91 Fed. Cl. 126, 137 (2010) (special master not obligated to discuss individually each of over 200 medical or scientific journal articles filed in an action, and the failure to do so did not lead to the conclusion that they were ignored). In most cases, discussion of a series of related articles (such as the literature submitted by Dr. Shafrir to support Petitioners' contention that components of the flu vaccine could have homology with epitopes in the brain, or epitopes associated with autoimmune reaction) are not extensively reviewed herein since my decision does not turn on an understanding or parsing of these articles. Indeed – my decision largely turns on my factual findings about L.V.'s condition and the onset of his developmental problems.

2013. *Id.* at 130, 214. Nor did Dr. Kendall ever specifically examine or evaluate L.V.; her opinion relied solely on test results performed by other treaters. *Id.* at 231.

Dr. Kendall characterized the diagnosis of mitochondrial disease as an "imperfect science" (tr. at 198), stating that it is "not an easy process, and it's not clean" (*id.* at 114), given limitations in the available tools to evaluate it, along with a general lack of a medical/scientific consensus as to the proper diagnostic criteria. *Id.* at 117, 119. Ultimately she embraced the Morava criteria applied by Dr. Frye in his diagnosis of L.V. Pet'rs' Ex. 10. She admitted, however, that there is actually no accepted set of criteria (based on scientific consensus) that can be used in diagnosing mitochondrial disease. Tr. at 119. In most cases, a definitive diagnosis of mitochondrial disease requires a muscle biopsy or confirmation by molecular testing aimed at looking for a possible genetic cause. *Id.* at 116-18, 146; Pet'rs' Ex. 41 at 9.

Dr. Kendall also acknowledged the evolving nature of the criteria (and specific tests) applied when attempting to diagnose a mitochondrial disease. Thus, Dr. Kendall noted that when the science for detecting mitochondrial diseases was less advanced, muscle biopsy tests were the "gold standard" diagnostic tool (Tr. at 241), but that more recently such tests were applied only to confirm a mitochondrial disease diagnosis (*id.* at 118), and that she herself rarely performs them. *Id.* at 119. She maintained that now there are many diagnostic tools available to test for mitochondrial disease more useful than the muscle biopsy. *Id*. at 118-19.

Based upon her review of the results of the many tests performed on L.V., along with his medical history, Dr. Kendall provided her opinion that the mitochondrial disease/dysfunction diagnosis for L.V., as first proposed by Dr. Frye and based upon his application of the Morava criteria, had evidentiary support. Tr. at 131-32. She acknowledged, however, that she did not accept the Morava number assigned to L.V. by Dr. Frye (nine points); rather, she would reclassify the total as six or seven,[37] meaning that (under Morava) the proper diagnosis for L.V. was only "probable" mitochondrial disorder[38] rather than definitive (a diagnostic classification that she indicated she would rarely accept, given the impossibility of confirming the diagnosis precisely). *Id*. at 144, 149-50; Pet'rs' Ex 10. To be more definitive in her diagnosis, Dr. Kendall stated that she would require either some kind of advanced genetic testing, to look for mutations that would directly impact mitochondrial function, or evidence that the patient's particular symptoms matched one of the more well-understood, and severe, forms of mitochondrial disease (such as Leigh disease). *Id.* at 200, 243 (discussing that genetic testing performed on L.V. was negative for mitochondrial disease).

[37] Dr. Kendall vacillated between denoting six or seven points on the Morava scale to L.V., although either score is sufficient to fall under its "probable" classification. Tr. at 143, 149-50.

[38] *See* Section IV(B) below for a discussion of Morava's points system.

Dr. Kendall agreed with Dr. Frye's analysis that L.V. was properly assigned three Morava "points" for clinical signs and symptoms. Thus, she found worthy of a Morava point the exercise intolerance that L.V. was reported to have displayed, pointing to his limited eye movement as evidence thereof. Tr. at 148. Yet, as Dr. Kendall acknowledged, there was little record evidence supporting this conclusion – going so far as to admit that her embrace of Dr. Frye's scoring for this Morava factor was wholly dependent on what the Vs had reported to treaters about L.V. rather than objective evidence, and that she herself did not believe based on her own review of those records that L.V. in fact had ever displayed any such weakness. *Id.* at 193-94, 245. She admitted the same with respect to L.V.'s purported low muscle tone (hypotonia), another factor relevant to the application of the Morava criteria (and indeed acknowledged that there were contrary reports in the medical records undermining the conclusion that L.V. displayed low muscle tone). *Id.* at 148, 194.

Dr. Kendall otherwise accepted the two additional points assigned by Dr. Frye in this category, based on L.V.'s alleged autistic regression (evidence of a CNS-related symptom)[39] and purported ongoing gastrointestinal tract illness (proof that L.V.'s disease was multi-systemic). [40] Tr. at 148. She also agreed with Dr. Frye's view of the significance of L.V.'s abnormal mitochondria morphology as seen via electron microscopy (a diagnostic factor worth two points on the Morava scale). Pet'rs' Ex. 41 at 7; Tr. at 197. Certain histological tests measuring mitochondrial proliferation also revealed a higher than normal mtDNA count. Tr. at 141-42. Dr. Kendall acknowledged that this particular diagnostic factor was not as closely correlated with mitochondrial dysfunction in children as a high nuclear DNA count (*id.* at 243), but insisted that it was a reasonable factor to be considered, and that the results in question were (taken together with the morphology observations) worthy of consideration. *Id.* at 198-99. Ultimately, she admitted that L.V.'s overall muscle biopsy results (pertinent to the "morphology" category) did not display any enzymatic abnormalities of his muscle tissue (tr. at 143), although she still maintained that the results suggested some form of mitochondrial dysfunction. *Id.* at 197-98.

Dr. Kendall did not, however, accept every aspect of Dr. Frye's application of the testing results under Morava. In particular, she substantively disagreed with Dr. Frye's point calculation with respect to the results of the enzymatic and metabolic tests. Thus, Dr. Frye gave L.V. the four

[39] Dr. Kendall acknowledged that the Morava criteria's inclusion of autism-like symptoms as evidence of an underlying mitochondrial disorder highlighted a circularity in the logic of Petitioners' causation theory offered in this case. Tr. 236-37. As Dr. Kendall admitted, individuals could be properly diagnosed with an ASD and not also have mitochondrial disease. *Id.* at 237. Yet here, the very same ASD symptoms being pointed to as evidence of the impact of the relevant vaccine were also being cited as evidence of the underlying condition that *caused* those symptoms. In effect, L.V.'s illness was proof of its cause.

[40] Dr. Kendall displayed some ambivalence, however, as to whether L.V.'s reported constipation was a factor suggesting the presence of a mitochondrial disorder, or merely reflective of the autistic regression that purportedly occurred in reaction to the vaccination. Tr. at 173-74.

point maximum under the Morava diagnostic framework for test results showing elevated lactate (two points), urinary tricarbon acid excretion (one point), and ethylmalonic aciduria (two points). Pet'rs' Ex. 24 at 1. Dr. Kendall, however, questioned the weight given by Dr. Frye to the elevated lactate finding because "it's not a true elevation from a biochemical mitochondrial perspective" and "we don't have any concurrent data to show whether it was a collection artifact." Tr. at 140. She therefore indicated that she disagreed with awarding a Morava point for the lactate results because concurrent tests of other enzyme levels (alanine to lysine ratios) did not corroborate them. *Id.* at 149. But she agreed with Dr. Frye that L.V. had high tricarboxylic acid excretion (tr. at 149), as well as high ethylmalonic acid levels, which (as corroborated by the fatty oxidation studies done on skin fibroblasts) were in her opinion suggestive of mitochondrial disease. *Id*. at 138-39. Thus she would have granted only two or three points for the test results relevant to this biomarker category.

More broadly, Dr. Kendall admitted (consistent with the manner in which she applied the Morava criteria) that any mitochondrial disease L.V. suffered from was on the mild end of the spectrum, and did not approach the severity of something like Leigh disease[41] (given, for example, the normal MRI readings obtained for L.V. (tr. at 202)) or other more easily diagnosed phenotypes. Thus, although she argued that mitochondrial diseases were "extremely variable" in their manner of development, the most obvious forms were progressive – but that she was not aware of any record evidence suggesting that L.V. had experienced a truly dramatic, downward progression in his symptoms post-vaccination. *Id.* at 188-90.

Dr. Kendall also acknowledged that her opinions about Dr. Frye's diagnosis arose from her own expertise and familiarity with the Morava criteria, and that she therefore did not particularly rely on much of the independent literature filed by the Petitioners in support of their claim, noting that some of it was not pertinent to L.V.'s circumstances.[42] Tr. at 207. However, she did in her

[41] Leigh disease is a subacute necrotizing encephalomyelopathy which is a type of "encephalopathy of unclear clinical and pathological criteria, causing neuropathologic damage like that of the Wernicke-Korsakoff syndrome. It occurs in two forms: the *infantile form* is caused by mitochondrial energy metabolism protein mutations and pyruvate carboxylase complex mutations and is characterized by degeneration of gray matter with necrosis and capillary proliferation in the brainstem; hypotonia, seizures, and dementia; anorexia and vomiting; slow or arrested development; and ocular and respiratory disorders, with death usually before age 3. The adult form usually first manifests as bilateral optic atrophy with central scotoma and colorblindness, followed by quiescent period of up to 30 years and then late symptoms such as ataxia, spastic paresis, clonic jerks, grand mal seizures, psychic lability, and mild dementia." *Dorland's* at 614.

[42] Thus, Dr. Kendall discussed one piece of literature that Petitioners highlighted as significant (Pet'rs' Ex. 41, Ref. 27 (J. Shoffner, et al., *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression*, 25(4) J. OF CHILD NEUROLOGY 429 (Jun. 2009) [hereinafter "Shoffner"]), because it suggested a relationship between fever and subsequent regression. Dr. Kendall, however, agreed that Shoffner involved a study of individuals who plainly had measurably high fevers lasting over a period of three to seven days – circumstances wholly distinguishable from the facts of this case. Tr. at 210-11.

testimony reference literature discussing the *Poling* case as supportive of the theory that young children with dysfunctional cellular metabolism may be prone to autistic regression if they simultaneously experience infections and immunizations (both "stressors" that could exacerbate an underlying mitochondrial disorder). Pet'rs' Ex. 41, Ref. 26 (J. Poling, et al., *Developmental Regression and Mitochondrial Dysfunction in a Child with Autism*, 21(2) J CHILD NEUROL 170-72 (2006); Tr. at 106, 136, 153, 155-56. While admitting that *Poling* was a single case rather than a verifiable, reproducible scientific study, she nevertheless placed great trust in what it revealed. *Id.* at 208-09, 212.

Based upon all of the above, Dr. Kendall proposed that Petitioners could meet all three of the prongs necessary to establish causation in a non-Table case under *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). First, Dr. Kendall offered the theory that the flu vaccine could sufficiently exacerbate an underlying mitochondrial disorder, synergistically reacting with an intercurrent infection,[43] to produce an autistic regression. Specifically, she opined that "the constellation of stressors" experienced by L.V. after receiving two flu vaccines plus his ear infection (tr. at 211) "had a synergistic effect on him that led to worsening of his – or aggravation of his underlying [mitochondrial] disorder or problem." *Id.* at 164-65.

To support this proposition, Dr. Kendall relied on literature discussing that vaccines can act as stressors for sufferers of mitochondrial diseases (tr. at 153-60), although she admitted that only isolated cases, or incidents involving well-understood and particularly severe forms of mitochondrial diseases such as Leigh disease, supported this element of her theory. *Id.* at 174. She also pointed to a paper filed by Petitioners but not relied upon in her report, indicating that "the influenza virus can, via a specific mitochondrial component . . . cause a cascade of events leading to apoptosis, which is a kind of programmed cell death." *Id.* at 162 (citing Pet'rs' Ex. 101 (A. Tran, et al., *Influenza Virus Induces Apoptosis via BAD-Mediated Mitochondrial Dysregulation*, 87(2) J. OF VIROLOGY 1049 (Jan. 2013)) [hereinafter "Tran"]). She then said that such a study made it more likely or plausible that the flu vaccine could cause an injury in a person with mitochondrial disease. Tr. at 163. Given the understanding that an infection can itself precipitate a regression or decompensation (*id.* at 155-56), she testified, the introduction of flu vaccine could similarly place stress on a patient with a preexisting mitochondrial disease. *Id.* at 165-66.

Second, Dr. Kendall testified that in fact the medical record confirmed that L.V. had been affected by the flu vaccine as she proposed. But she was generally unable to reference evidence from that record in support of this assertion. Tr. at 178-79, 184-86. At best, Dr. Kendall vaguely cited to reports of L.V.'s loss of words or irritability, but could not recall much else. *Id.* at 170-72.

[43] Notably, on this aspect of her testimony Dr. Kendall diverted somewhat from her original expert report, which suggested that the flu vaccine alone had produced L.V.'s regression, rather than in concert with his ear infection. *Compare* Tr. 231-32 *with* Pet'rs' Ex. 42 at 11.

She also admitted that the speech delay as reported by the Vs on December 13, 2006, was not itself strong proof of a dramatic, vaccine-induced regression caused by an underlying mitochondrial disease (*id.* at 180), and that L.V.'s constipation and related problems were ongoing, having been present prior to his receipt of the flu vaccine. *Id.* She further agreed that ASD features, development delays, developmental regression, and constipation are symptoms that are often seen independent of a mitochondrial disorder. *Id.* at 196-97. Indeed, Dr. Kendall admitted on cross-examination that, given the paucity of evidence suggesting an immediate, post-vaccination regression, her overall theory would be undermined if it were determined that L.V.'s developmental regression began before he received the flu vaccine. *Id.* at 184-86.[44] However, because it was her opinion that whatever mitochondrial dysfunction L.V. had was mild in form, it would not be likely (in her opinion) that his regression would be as evident as in cases where a child unquestionably was experiencing one of the more severe forms of the disease, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes ("MELAS").[45] *Id.* at 196-97.

Finally, Dr. Kendall asserted that the timeframe from the December 8, 2006, administration of the second dose of flu vaccine to L.V.'s alleged developmental regression was medically acceptable. Under Dr. Kendall's proposed theory, onset of regression would occur in seven to ten days – a length of time she derived from a single piece of literature involving a retrospective study of individuals suffering from mitochondrial disease, some of whom experienced developmental regression as is alleged to have occurred with L.V. Tr. at 166-69; Pet'rs' Ex. 84 at 6 (J. Edmonds, et al., *The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration with Infection*, 128 ARCH. OTOLARYNGOL. HEADNECK SURG. 355 (Apr. 2002) [hereinafter, "Edmonds"] (setting forth that in most patients the neurologic event occurred three to seven days after onset of infection)). Approximately one week after L.V.'s second flu vaccination, there was "some question about some neurological changes or problems or certainly by his parents' report of changes in his irritability." Tr. at 169-70. Although Dr. Kendall admitted that irritability was not particularly strong evidence of an encephalopathy, when viewed in context

[44] Dr. Kendall also made some attempt to address the fact that Petitioners' theory required L.V. to have suffered from a mitochondrial disease prior to his receipt of the flu vaccine. Thus, she indicated that it was not surprising to her that L.V. might have begun to display some symptoms of autism before he received the flu vaccine, since a child suffering from some form of a preexisting mitochondrial disease would experience ASD-like symptoms regardless of the role a vaccine played in those symptoms' exacerbation. Tr. at 136.

[45] MELAS is a condition that "affects many of the body's systems, particularly the brain and nervous system and muscles." Symptoms include "muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures." *Mitochondrial Encephalomyopathy, lactic acidosis, and stroke-like episodes,* GENETICS HOME REFERENCE, (Dec. 2013), http://ghr.nlm.nih.gov/condition/mitochondrial-encephalomyopathy-lactic-acidosis-and-stroke-like-episodes (last visited Feb. 11, 2016).

with L.V.'s purported subsequent skill loss, in her opinion it was proof of the existence of a "regressive encephalopathy" that was "certainly temporally related." *Id.* at 170-172, 176.

2. Dr. Yuval Shafrir

Dr. Shafrir is a child neurologist who graduated from the Sackler School of Medicine at the Tel Aviv University in 1982. He thereafter did residencies in pediatrics at Kaplan University and the Bellinson Medical Center in Israel. Tr. at 252-53; Pet'rs' Ex. 81 at 2. Dr. Shafrir went on to do residencies in pediatrics at North Shore University Hospital in New York, and in pediatric neurology at the Washington University Medical Center in Missouri. Tr. at 254; Pet'rs' Ex. 81 at 2. From 1992 to 2000, Dr. Shafrir worked at a number of different U.S. hospitals, but currently practices pediatric neurology in private practice affiliated with Sinai Hospital in Baltimore, Maryland. Tr. at 252. He is licensed to practice medicine in Maryland, and has board certifications in child neurology, although he has not renewed his board certification in pediatrics. *Id.* at 252, 322, 334. He has worked and taught across the country in pediatrics and neurology, and presently does so at the University of Maryland School of Medicine. Pet'rs' Ex. 81 at 4. He has also written extensively on issues of pediatric neurology. *Id*. at 4-8.

Dr. Shafrir testified as an expert in pediatric neurology. Tr. at 252. He is not an expert in immunology or mitochondrial disease, however. *Id.* at 268, 321, 361-62, 380. He is also not one of L.V.'s treating physicians, and has never examined L.V. himself. *Id*. at 404. Dr. Shafrir sees approximately 300 patients per month. Tr. at 252-54, 402. Mostly, he treats headaches and seizures, but twenty percent of his practice is developmental in nature, and approximately ten percent of his patients have an ASD diagnosis. *Id*. at 252-54, 402. But he does not have clinical experience studying ASDs, nor does he possess specific research experience or training in that specialty. *See generally* Pet'rs' Ex. 81.[46]

Dr. Shafrir offered brief testimonial support for Dr. Kendall's theory that L.V.'s autism was related to his alleged preexisting mitochondrial disease. Tr. at 267-68, 317-18; Pet'rs' Ex. 193 at 3. The vast majority of his testimony, however, related to his own, alternative causation theory, which was somewhat confusing and extremely wide-ranging. Dr. Shafrir's opinion began with a distinction he drew between autism that proceeds on a natural course and the "regressive autism"

[46] Dr. Shafrir was passionate in defending his opinions at hearing – but some of that passion was lacking in scientific grounding. Thus, Dr. Shafrir acknowledged his belief that today, autism is present in the United States and the world more generally at epidemic levels that cannot be explained by genetic factors ("genetics cannot occur in epidemics" Tr. at 295; *see also Id.* at 257, 259, 330-31, 403. He did not, however, offer reliable evidence suggesting that the scientific community of ASD experts shares his opinion, let alone that his opinion about an "autism epidemic" is scientifically well-founded. He similarly denied the possibility that the rise in ASD diagnoses could be explained by the fact that medical practitioners have become better at spotting and diagnosing the relevant behaviors and/or symptoms, claiming that "any preschool teacher" can make the diagnosis. Pet'rs' Ex. 80 at 31.

he believes L.V. experienced. Tr. at 336. Indeed, he disputed the concept of a "natural course of autism" that would typically include a developmental regression. *Id.* at 329. Rather, according to Dr. Shafrir, sudden autistic regression is more likely caused by an encephalopathy. *Id*. at 251. He thus maintained that regressive autism – which in his view accounts for approximately thirty percent of all ASD patients, and is in some cases treatable (due to its causes) – was a form of autism, although he admitted that it does not constitute a separate clinical phenotype that is formally recognized medically. *Id*. at 336-37.

In Dr. Shafrir's opinion, L.V. experienced an "acute autistic regression following his second influenza immunization" (tr. at 264) at 20 months (*id*. at 338) which "can be best explained as an autoimmune process." *Id*. at 264-65, 274. He based this view on post-vaccination evidence, which he argued revealed "all the components" of autistic regression. *Id*. at 280. His opinion was also based on scientific articles and literature that he maintained drew a connection between the administration of the flu vaccine and L.V.'s allegedly abrupt subsequent regressive incident.

First, Dr. Shafrir testified that the flu vaccination has been demonstrated to be a cause of autoimmune encephalopathy. Tr. at 284; Pet'rs' Ex. 80 at 28. As proof, he mentioned several pieces of literature associating vaccines (and particularly the flu vaccine) with antibody-mediated autoimmune encephalitis. Tr. at 284 (citing Pet'rs' Ex. 80, Ref. 10 (J. Dalmau, *Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis*, 10 LANCET NEUROL 63 (Jan. 2011) [hereinafter "Dalmau"]); Pet'rs' Ex. 80, Ref. 11 (T. Hung, et al., *Anti-N-methyl-D-Aspartate Receptor Encephalitis*, 52 PEDIATRICS & NEUROLOGY 361 (Jan. 2011)); Pet'rs' Ex. 80, Ref. 12 (M. Kubota and Y. Takahasi, *Steroid-Responsive Chronic Cerebellitis with Positive Glutamate Receptors δ2 Antibody*, 23(2) J. OF CHILD NEUROLOGY 228 (Feb. 2008)); and Pet'rs' Ex. 80, Ref. 13 (J. Takanashi, et al., *Late Delirious Behavior with 2009 H1N1 Influenza: Mild Autoimmune-Mediated Encephalitis?* 129 PEDIATRICS 1068 (2012)). He maintained that scientific studies have plainly observed a tendency in individuals to develop autoantibodies following receipt of the flu vaccine. Pet'rs' Ex. 80 at 30 (citing Pet'rs' Ex. 80, Ref. 31 (N. Toplak, et al., *Autoimmune response following annual influenza vaccination in 92 apparently healthy adults*, 8 AUTOIMMUNITY REVIEWS 134 (2008)). Such autoantibodies, in turn, attack human brain tissues, resulting in an encephalopathic incident. Tr. at 208 (citing Pet'rs' Ex. 41, Ref. 26 (E. Hsiao, et al., *Modeling an autism risk factor in mice leads to permanent immune dysregulation*, PROC. OF THE NAT'L ACAD. OF SCI. www.pnas.org/cgi/doi/10.1073/pnas.1202556109)[47]; Tr. at 301; Pet'rs' Ex. 80, Ref. 19 (D. Obregon, et al., *Potential Autoepitope within the Extracellular Region of*

[47] "Developmental Regression and Mitochondrial Dysfunction in a Child with Autism" is a case abstract of one child who experienced severe regression following a vaccination. Petitioners have attempted on numerous occasions to equate L.V.'s situation with that of the child in *Poling*. *See, e.g.*, Motion to Compel Respondent's Admission of the Medical Theory, Jan. 5, 2015 (ECF No. 112). However, *Poling* was a severe example of a Table Injury following vaccination, unlike the non-Table claim here.

Contactin-Associated Protein-like 2 in Mice, 4(1) BRITISH J. OF MED. & MED. RES. 416 (2014) [hereinafter "Obregon"]))[48]; Tr. at 297 (citing Pet'rs' Ex. 80, Ref. 14 (R. Dhamija, et al., *Neuronal Voltage-Gated Potassium Channel Complex Autoimmunity in Children*, 44 PEDIATR NEUROL 44 (2011) [hereinafter "Dhamija"])[49]). Thus, Dr. Shafrir maintained that the flu vaccine could in theory produce an autoimmune reaction through the creation of antibodies and/or active T-cells which cross-react with certain proteins in the brain. Tr. at 361 (citing Pet'rs' Ex. 80 at 31). This "more likely than not" causes "widespread disruption of the brain function, resulting in autism." Tr. at 294, 296, 331.

For additional support, Dr. Shafrir referenced literature highlighting instances in which vaccines have been associated with negative neurologic conditions. Tr. at 287-89; Pet'rs' Ex 80, Ref. 5 (K. Lapphra, et al., *Adverse Neurologic Reactions After Both Doses of Pandemic H1N1 Influenza Vaccine With Optic Neuritis and Deymyelination*, 30(1) THE PED. INFECTIOUS DISEASE J. 84 (Jan. 2011) [hereinafter, "Lapphra"]). Lapphra describes a case study showing the occurrence of neurologic changes in a two-year-old Filipino boy shortly after receiving the H1N1 flu virus vaccine. *Id*. at 18-19. The child was diagnosed with acute disseminated encephalomyelitis ("ADEM")[50]; his initial symptoms had spontaneously resolved after the first dose of vaccine, but worsened after the second. *Id*. at 19. The Lapphra authors claimed the displayed progression in symptom development strongly suggested that the flu vaccine was a causative factor for the child's illness, arguing that the sequence of events was consistent with the production of greater amounts of myelin-attacking antibodies after each vaccination. *Id*. Here, by contrast, L.V.'s regression has never been attributed to ADEM, nor was he ever diagnosed with that or any other similar demyelinating disease. In addition, the H1N1[51] flu vaccine at issue in Lapphra is not precisely analogous to the vaccine L.V. received herein, further limiting the relevance of this case study to L.V.'s circumstances. Tr. at 363-66.

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[48] Dr. Shafrir referenced Obregon numerous times throughout his testimony. Even though the study solely evaluated how human viral and bacterial wild pathogens can trigger the creation of antibodies that attack certain brain proteins, resulting in an encephalopathy, Dr. Shafrir suggested that a similar homology existed between components of the flu vaccine and those same proteins, and thus the same result was possible. Tr. at 405-06.

[49] Dr. Shafrir referenced Dhamija as evidence that influenza vaccinations cause an autoimmune attack on the brain that produced autistic regression. Tr. at 297. This article, however, mentions only a single example of such an association (Pet'rs' Ex. 80, Ref 14 at 2) and concludes that larger case studies are necessary. *Id*. at 7.

[50] ADEM is an acute or subacute inflammation involving both the brain and spinal cord characterized by perivascular lymphocyte and mononuclear cell infiltration and demyelination. "[I]t occurs most often after an acute viral infection…but may occur without a recognizable antecedent. It is believed to be a manifestation of an autoimmune attack on the myelin of the central nervous system. Symptoms include fever, headache, and vomiting; sometimes tremor seizures, and paralysis; and lethargy progressing to coma that can be fatal." *Dorland's* at 613.

[51] As Dr. Shafrir admitted on cross, strains of the H1N1 virus were not added to the seasonal flu vaccine until 2010 – four years after L.V. received the flu vaccine. Tr. at 366.

Dr. Shafrir next opined that autoimmune encephalitis (as well as immune dysfunction more generally) is a recognized cause of regressive autism. Tr. at 285; Pet'rs' Ex. 80 at 30-31. As exemplifying a portion of the "accumulating evidence" that an autoimmune process can start in the brain and precipitate autism, he pointed to a series of case studies: one of which occurred in a child with Voltage-Gated Potassium Channel ["VGKC"][52] antibodies (Dhamija), and two others where the patients had measurably heightened levels of anti-NMDA-receptor[53] antibodies, which have been linked to a specific kind of encephalitis.[54] *See* Pet'rs' Ex. 80, Ref. 15 (O. Scott, et al., *Anti-N-Methyl-d-Aspartate (NMDA) Receptor Encephalitis: An Unusual Cause of Autistic Regression in a Toddler*, J. OF CHILD NEUROLOGY 1 (2013)), and Ref. 16 (C. Creten, et al*., Late onset autism and anti-NMDA-receptor encephalitis*, 378 LANCET 98 (2011)). He also referenced an article that speculates about the possible relationship between autoimmune synaptic encephalitis and autism. Tr. at 376-77 (*citing* Pet'rs' Ex. 80, ref. 18, M. Kayser, et al., *The Emerging Link Between Autoimmune Disorders and Neuropsychiatric Disease*, 23(1) NEUROPSYCHIATRIC CLIN. NEUROSCI. 90 (Winter 2011) [hereinafter "Kayser"]); *see also* Pet'rs' Ex. 80 at 29.

However, Dr. Shafrir acknowledged limitations to the portion of his theory connecting the flu vaccine to autoimmune-mediated encephalopathies. On cross-examination, Dr. Shafrir admitted that the literature he cited (and in particular, Dalmau) observed no more than an association between the flu vaccine and encephalopathy, and thus did not support the conclusion that the flu vaccine was *itself causative* of any form of encephalopathy. Tr. at 366-67, 370. He also conceded that, because there is no evidence that L.V. has anti-NMDA encephalitis, anti-NMDA antibodies, or anti-VGKC encephalitis or antibodies, studies focusing on such narrow forms of autoimmune illnesses were largely inapposite. *Id*. Indeed, as Dr. Shafrir admitted, L.V. displayed no objective evidence of an autoimmune reaction in his brain, and no MRI findings that would be associated with an autoimmune encephalopathy. *Id.* at 362-63, 369, 508. Dr. Shafrir nevertheless stressed there were individual case studies where regression associated with an encephalopathic event had occurred, and that such regressions could be treated. *Id.* at 373-75.

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[52] As noted in Dhamija, voltage-gated potassium channels are proteins in neurons in the central and peripheral nervous systems that play a role in membrane repolarization, axonal conduction, and synaptic transmission. Dhamija at 275.

[53] NMDA stands for "N-methyl-d-Aspartate." NMDA is a "neurotransmitter similar to glutamate, found in the central nervous system; a synthetic preparation is used experimentally to study the excitatory mechanisms of glutamate transmitters." *Dorland's* at 1152.

[54] Anti-NMDA receptor encephalitis is a clinical disorder, mostly in adolescents, that presents with a sudden onset of altered mental status, with and without seizures, behavior change, often fever, and ovarian or testicular tumors. Tr. 515-16.

To explain the biologic mechanism by which the flu vaccine could precipitate an autoimmune encephalopathy as Petitioners alleged to have happened with L.V., Dr. Shafrir proposed molecular mimicry through homology of epitopes.[55] Tr. at 267; Pet'rs' Ex. 80 at 29-30 (citing Obregon). In a typical immune response, he explained, cells produce antibodies in reaction to the viral or bacterial invader. Tr. at 301, 405. However, due to similarities (the "mimicry") in the structure of the amino acid sequences in the healthy tissue and the virus, the antibodies produced mistakenly attack healthy tissue (as well as the virus they were intended to attack), thus triggering an autoimmune reaction. *Id*. at 405. The same process could occur with vaccination; as evidence, Dr. Shafrir offered specific literature that demonstrated homology between components of the flu vaccine and brain tissues. *Id.* at 298-99. In particular, Dr. Shafrir discussed the homology between the amino acid sequence in the CSPR-2 protein[56] found in the brain and the hemagglutinin protein of influenza A virus, which he maintained have been found by reputable studies to be sufficiently similar to cross-react and thereby create the necessary autoantibodies to attack self, and which he purported is a component of the flu vaccine.[57] *Id*.

In further support of his proposed molecular mimicry mechanism (and also as evidence of the pathogenic potential of the flu vaccine), Dr. Shafrir cited a Finnish study involving narcolepsy among children after receipt of the H1N1 Pandemrix flu vaccine, along with other literature addressing the same event. *See, e.g.*,Tr. at 291; Pet'rs' Ex. 80 at 31 (citing Pet'rs' Ex. 80, Ref. 33 (A. Käll, *The Pandemrix – narcolepsy tragedy: how it started and what we know today*, 102 FOUNDATION ACTA PAEDIATRICA 2 (2013)); Pet'rs' Ex. 80, Ref. 34 (M. Partinen, *Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination*, 13 LANCET NEUROL 600 (2014));, Pet'rs' Ex. 80, Ref. 35 (M. Partinen, et al., *Does autoreactivity have a role in narcolepsy?*, 13 LANCET NEUROL 1072 (Nov. 2014)); and Pet'rs' Ex. 80, Ref. 36 (A. Singh, et al., *Genetic association, seasonal infections and autoimmune basis of narcolepsy*, 43 J. AUTOIMMUN. 26 (Jun. 2013)). However, Dr. Shafrir admitted that the formulation of the Pandemrix vaccine was not equivalent to what L.V. received (and indeed is not even administered in the U.S. (tr. at 365)),

[55] As Dr. Shafrir explained, "epitope" is a term in immunology to describe a short segment of an amino acid that can produce an immune reaction to an antigen. Tr. at 267. He argued that the best example of how molecular mimicry worked in L.V.'s case was provided by the studies that show a relationship between the H1N1 vaccination and narcolepsy. *Id*. at 291.

[56] Dr. Shafrir explained that CSPR-2 protein is one of the two major proteins (the other being Lg-1) that are targets for an autoimmune attack. Tr. at 301. Antibodies against this particular protein could, according to Dr. Shafrir, precipitate symptoms related to autism. *Id*. at 302.

[57] Dr. Shafrir specifically testified that the influenza-a and influenza-b components were both present in the flu vaccine L.V. received, but it was the homology between hemagluttinin protein in the influenza-a virus and the CSPR-2 protein in the brain that caused the autoimmune reaction. Tr. at 300-02. Although L.V.'s brain had never been tested for these proteins, Dr. Shafrir maintained that this component of his theory still had plausibility. *Id*. at 302-03.

although he nevertheless maintained that, because both versions had some of the same protein sequence components, the study still had relevance to his theory. *Id.* at 366.

Dr. Shafrir also maintained that an individual like L.V. could be especially sensitive to stimulation by the flu vaccine given other aspects of his overall health. Tr. at 318, 380-81; Pet'rs' Ex. 190 (G. Morris, et al., *The Many Roads to Mitochondrial Dysfunction in Neuroimmune and Neuropsychiatric Disorders*, 13 BIOMED CENTRAL 68 (2015)). Thus, Dr. Shafrir asserted that L.V. was immunosensitive (tr. at 285-86), having obvious abnormalities in his immune system, as evidenced by his multiple, severe allergies, high erythrocyte sedimentation rate, documented IgA deficiency, and inflammatory bowel disease diagnosis. *Id*. at 285-86, 296; Pet'rs' Ex. 80 at 27. He emphasized that patients who are susceptible to immune abnormalities are more likely to suffer autoimmune reactions. Tr. at 323 (citing Pet'rs' Ex. 187 (Y. Takahashi, et al., *Vaccination and infection as causative factors in Japanese patients with Rasmussen syndrome: Molecular mimicry and HLA class I* 13(2-4) CLINICAL & DEVELOPMENTAL IMMUNOLOGY 381 (Jun.-Dec. 2006))). Individuals with allergies are also more likely to be autistic. *Id*. However, he admitted that he could cite no objective evidence from the record of L.V.'s purported immune-sensitivity, and that (once again) existing MRI findings did not support this aspect of his theory. Tr. at 362-63.[58]

Based upon the above, Dr. Shafrir offered an interpretation of L.V.'s medical history aimed at demonstrating that the regression L.V. experienced appeared suddenly, after L.V.'s second flu vaccination. He maintained that the medical record showed that L.V. was developing normally until December 8th, with a sudden and severe regression thereafter, beginning within a week (or around the time of the December 13th pediatric visit). Tr. at 268-69, 339. Yet Dr. Shafrir admitted that he lacked data from the medical record that substantiated this assertion, beyond some mention of constipation and the ear infection L.V. was experiencing at the time. *Id.* at 342-44. He could point to little else in the record (beyond the Vs' recollections) that L.V. ever experienced anything medically dramatic, in this period or thereafter.

Dr. Shafrir also attempted to grapple with contrary evidence in the record suggesting that L.V.'s ASD symptoms were evident before he received even the first flu vaccine. Thus, he admitted that L.V.'s medical records were "all over the place," in identifying the onset of his alleged regression and/or ASD symptoms. Tr. at 328, 409. However, he posited that the Vs became "very concerned" about L.V.'s development only at 21 months, downplaying the significance of pre-vaccination evidence of developmental problems they may have observed (and reported to treaters as having occurred at 18 and 19 months – before receipt of the first dose of the flu vaccine).

[58] At best, Dr. Shafrir proposed that L.V. likely possessed a genetic defect inherited from his parents (as evidenced by a gene "deletion that was found in [L.V.'s] father" (tr. at 296)), offering additional literature to support the conclusion that autistic children with demonstrated allergies more likely also suffer from immune system abnormalities. *Id*.

Id. at 277-78, 347, 387. Thus, Dr. Shafrir proposed that the Vs likely mistook normal childhood behaviors, such as flapping (which the medical records show was observed at 12 months), as the first signs of autism. *Id*. at 277-78, 347-58.

Dr. Shafrir similarly attempted to rebut the many instances in the medical record, beginning in January 2007, where the Vs directly informed a treater (such as Dr. Coplan) that L.V.'s developmental regression had been evident at 18 months of age rather than 21 months. Tr. at 347. To do so, he persistently relied on a pediatric well-child visit record from September 2006, which reported that L.V. was, at that time, a "normal child," as well as Mrs. V's testimony. *Id*. at 281. Dr. Shafrir characterized all subsequent, contrary medical records that referenced an earlier start to L.V.'s autism symptoms as "profoundly wrong." *Id.* at 348. But Dr. Shafrir was generally unsuccessful in his efforts to explain why such records were untrustworthy.[59] He otherwise categorically dismissed the many contemporaneous statements about L.V.'s onset of symptoms as instances in which the Vs simply repeated a "story" about L.V.'s onset by rote. *Id.* at 324-25, 350-51, 356.[60]

Ultimately, Dr. Shafrir opined that the flu vaccine was the "only obvious cause" of L.V.'s regression. Tr. at 283; Pet'rs' Ex. 80 at 31. In so determining, he rejected the possibility of some underlying genetic or other environmental explanation. Tr. at 294, 296. Indeed, Dr. Shafrir went so far as to reject genetic causes of autism in general, stating that "genetics cannot occur in epidemics." *Id.* at 295.[61]

In an attempt to support Petitioners' overall burden of demonstrating a medically acceptable timeframe between vaccination and onset of L.V.'s autistic regression, Dr. Shafrir

[59] For example, Dr. Shafrir questioned a statement set forth in Dr. Coplan's January 23, 2007**,** record regarding L.V.'s purported delay in use of a spoon and/or cup to feed, pointing out that a contemporaneous record from a 12-month visit suggested that L.V. had by that time already mastered spoon-feeding (thus not only calling into question the accuracy of Dr. Coplan's record but also suggesting the degree of L.V.'s post-vaccination regression). Tr. at 397-400. As discussed below, however, even if this part of Dr. Coplan's evaluation is inconsistent with an earlier record (a conclusion I do not adopt given other records), I do not find that it is *meaningfully* so, such that I would find Dr. Coplan's January 2007 written evaluation overall untrustworthy in the manner urged by Petitioners.

[60] Thus, Dr. Shafrir was cross-examined about several specific such instances in the medical record from 2007 and into 2008, where the Vs were reported to have specified an earlier onset of L.V.'s ASD regression and/or symptoms. In every case, Dr. Shafrir disputed the record's accuracy. *See, e.g.*, Tr. at 347, 350, 351, 353 (disputing references to regression beginning at 18 months in the Early Intervention evaluation (Pet'rs' Ex. 13 at 8); the Vs' report to Dr. Coplan (Pet'rs' Ex. 5 at 3); reports to Dr. Brian Jepson at the Thoughtful House in Austin, Texas (Pet'rs' Ex. 10 at 78); Dr. Hillary Kruger's records in May of 2007 (Pet'rs' Ex. 6 at 1); Dr. Arthur Krigsman's records in June of 2007 (Pet'rs' Ex. 9 at 6); and Dr. James Neubrander's chart in September of 2007 (Pet'rs' Ex. 8 at 3)).

[61] Dr. Shafrir later, however, admitted that the interaction of environmental factors with a genetic predisposition is, in his view, the most likely cause of autism in the majority of cases. Tr. at 404.

argued that there was evidentiary support from the medical record for the conclusion that a reaction occurred within five days. Tr. at 278, 280, 289-90. He based this argument in part on the fact that L.V. had already received the first dose of the flu vaccine in November, which he claimed played "an obvious role" because "[p]rimary immune reaction cannot occur in five days." *Id*. at 292-93. He thus differentiated these circumstances from the typical conception of "symptomatic rechallenge,"[62] instead asserting that this was an instance of what he termed "immunological rechallenge." *Id*. at 305-06. Immunological memory from the first vaccination facilitated the molecular mimicry and the production of antibodies which acted against parts of the brain, causing autism. *Id.* at 285. In further support of the reasonableness of the time period from vaccine to injury, Dr. Shafrir noted that neurological loss can occur within a couple of days and usually within a week to ten days. *Id*. at 169. In this regard, he compared L.V.'s regression to the development of narcolepsy and/or Guillain-Barré syndrome both of which can manifest within 72 hours of a trigger event. *Id*. at 289-91.

Again, however, Dr. Shafrir had difficulty identifying record support for this aspect of his opinion. He thus admitted that he could point to very little record evidence actually establishing the profound regression he posited that L.V. had experienced in December, beyond statements contained in Dr. Coplan's assessment about behavioral and developmental changes that the Vs had observed in L.V. – records he simultaneously attacks as inaccurate or inconsistent with the Vs' view of L.V.'s history. Tr. at 343. At most, he referenced evidence of L.V.'s constipation around the time immediately after the December 8th vaccination. *Id.* at 344-46.

C. Respondent's Expert – Dr. Bruce Cohen

Respondent's expert, Bruce Cohen, M.D., offered testimony mostly responding to Petitioners' theory that L.V. suffered from a mitochondrial disease or disorder of some kind that related to his alleged post-vaccine 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). Resp't's Ex. B at 2. Dr. Cohen 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 was previously board-certified in Pediatrics. *Id.* at 3.

[62] According to Dr. Shafrir, the typical concept of rechallenge is a symptomatic rechallenge, where an individual has a reaction to a medicine or a vaccination, and then has a similar or worse reaction after the second exposure to the medicine or vaccine. Tr. at 305-06.

Dr. Cohen 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 3; Tr. at 414. He has also taught courses specifically on mitochondrial disease in symposia. Resp't's Ex. B at 5-6. He is a reviewer for several journals and on the editorial board for the Mitochondrion and the Pediatric Neurology Journal. *Id.* at 4. And he serves on various review committees – seven in total – including the Neurofibromatosis Consortium. *Id.* Dr. Cohen has written extensively on issues of mitochondrial diseases, authoring or co-authoring nearly 100 peer-reviewed articles. *See generally*, *id*. Dr. Cohen has served in many different capacities for The United Mitochondrial Disease Foundation since 1999 and served on many different committees regarding mitochondrial disease. *Id*. at 4-5.

Dr. Cohen has particular expertise in studying and treating mitochondrial diseases. He has been assisting with or treating patients with mitochondrial disorders or suspected mitochondrial disorders since 1994. Tr. at 415. As a child neurologist, Dr. Cohen sees adults and children with mitochondrial diseases and brain tumors. *Id.* at 412. Although Dr. Cohen does not diagnose ASDs, some of his patients have autism as well as suspected mitochondrial diseases. *Id.* at 417. He routinely diagnoses mitochondrial diseases or dysfunction in his patients, estimating that he has seen several thousand patients in which the disease was suspected, or actually diagnosed, since 1994. *Id.* at 416. Of the nearly 100 peer-reviewed articles he has published, approximately a fourth of them are readily discernible as dealing primarily with issues of mitochondrial dysfunction. *See generally*, Resp't's Ex. B.

Relying on his experience treating patients with mitochondrial diseases, Dr. Cohen formulated his opinion after reviewing L.V.'s medical records and the expert reports and journal articles filed, along with Petitioners' expert reports. Resp't's Ex. A at 4; Tr. at 423. Based on this review, Dr. Cohen opined that there is no credible evidence that L.V. has a mitochondrial illness, or that any vaccination L.V. received in any way contributed to his autism or other medical conditions. Resp't's Ex. A at 4.

Dr. Cohen began by providing an overview of mitochondria, and the function they play in the generation of energy necessary for the human body. Tr. at 424. He explained that mitochondria exist in all mammalian cells, except for mature red blood cells. *Id.* at 425. Mitochondria are one micron in length, or one-forty-thousandth of an inch, and have an outer membrane and an inner mitochondrial membrane. *Id*. The mitochondria generate energy, or adenosine triphosphate ("ATP"),[63] which is held in covalent bonds, and some metallic molecules within the mitochondria conduct the electricity via the ETC. *Id* at 428. The ETC is found within the inner mitochondrial

[63] Adenosine triphosphate is a nucleotide involved in energy metabolism, which occurs in all cells and is used to store energy. *Dorland's* at 30.

membrane and allows for the regeneration of ATP, which can then be used by the cells throughout the human body to cause muscle contractions, allow the ears to hear, or even cause the heart to beat. *Id.* at 429. This process also creates heat and free radicals that can damage the cell or serve "healthful purposes" within the body. *Id.*

Because not all mitochondrial diseases are the same, not every patient displays the same symptoms, though there are some classic phenotypes. Tr. at 430. Mitochondrial diseases were described as early as 1930, and since that time the diagnostic criteria used to discern if an individual suffers from such a disease have been refined. *Id.* at 429-30. The development of genetic testing, however, has increased the surety of the diagnosis, lessening the reliance on muscle biopsies or enzymology,[64] which were in the past the best ways to confirm a suspected mitochondrial disease. *Id.* at 430, 432, 462.

Dr. Cohen discussed the differences between primary and secondary mitochondrial disease. Tr. at 434. Primary mitochondrial disease refers to those diseases that have a "known, verified genetic cause that is linked to the clinical phenotype of the patient" and "primarily affect the mitochondrial structure." *Id.* Although primary mitochondrial dysfunction can be most directly diagnosed by genetic testing, it can still be properly diagnosed even in the absence of such testing if the patient's symptoms match a known phenotype, such as Leigh disease. *Id.* at 435-36. Secondary mitochondrial disease usually involves a problem external to the mitochondria that indirectly produces metabolic dysfunction, such as a genetic defect that causes iron not to be processed properly, with the excess iron harming the mitochondria. *Id.* at 435-36, 595. Dr. Cohen also discussed mitochondrial dysfunction, which he defined as a "global, generic term" referring to when the mitochondria work imperfectly or are overloaded, but not necessarily as the result of disease. *Id.* at 435-36. Such mitochondrial dysfunction can occur in otherwise benign, everyday contexts (*i.e.* eating a high-fat meal). *Id.* at 436.

To diagnose a mitochondrial disease, Dr. Cohen proposed, a physician should begin with a patient's medical history, including a physical exam and family history. Tr. at 432. If the patient fits a known mitochondrial disease phenotype, then the physician should conduct tests of the blood, urine, and cerebral spinal fluid for indication of the mitochondrial process. *Id.* at 433. While some biochemical markers on their own may suggest dysfunction, Dr. Cohen proposed that review of biomarker test results should be considered collectively rather than in isolation. *Id.* at 461, 477. The physician should also do a functional organ test, depending on which organ(s) the physician suspects the mitochondrial disease may be affecting. *Id.* Other factors indicative of an ongoing

[64] Enzymology is "the study of enzymes and enzymatic action." *Dorland's* at 629.

disease process are evidence of too few mitochondria or (in the case of adults) too few mtDNA. *Id.* at 460.

A muscle biopsy with electron or light microscopy testing can also be performed to confirm the presence of a mitochondrial disease. Tr. at 452. Through electron microscopy, a piece of muscle is processed and then magnified 25 to 40,000 times. *Id.* at 456. In light microscopy, by contrast, a pathologist takes a piece of muscle, slices it into thin sections for staining with different stains, sometimes at different pH levels, and then looks at it under an ordinary microscope to make a diagnosis. *Id.* at 452-53. As science has evolved, however, the emphasis placed on the importance or meaning of certain tests used to diagnose mitochondrial disease has changed, Dr. Cohen indicated. Thus, because over the past several years genetic testing capable of reliably confirming a mitochondrial disease has become more widely available, the significance of muscle biopsies and other tests have greatly diminished. *Id.* at 434.

One recent piece of literature Dr. Cohen co-authored and emphasized as particularly useful in understanding what factors are most suggestive of the existence of a mitochondrial disease is R. Haas, et al*., Mitochondrial Disease: A Practical Approach for Primary Care Physicians,* 120 PEDIATRICS 1326 (2007), filed as Ct. Ex. 1. ECF No. 133.[65] Dr. Cohen noted that Haas differentiates between "red flag" indicia of the presence of mitochondrial disease versus what the article terms 'nonspecific" criteria. *Id*. at l; Tr. at 431-32, 470-72. In effect, the nonspecific criteria are far less persuasive evidence of the presence of mitochondrial disease than the red flag indicia because they are not exclusively or predominantly associated with mitochondrial disease. Tr. at 446.

Dr. Cohen provided examples of the ways in which certain nonspecific criteria (that in the past might have been given more weight in making a mitochondrial disease diagnosis) were not particularly useful in signifying the presence of the disease. Thus, Dr. Cohen noted that the gastrointestinal dysfunction commonly experienced by individuals with an ASD was not commensurate with the far more severe kind of gastrointestinal symptoms those with classic phenotypes of mitochondrial diseases experienced. Tr. at 441-44. Similarly, the level of brain injury suffered in autism was not nearly as progressively debilitating and monophasic as that experienced by someone diagnosed with Leigh disease (whose brain injuries and other symptoms would in most cases result in death – not the outcome inevitably experienced by those diagnosed with an ASD). *Id.* at 434, 439.

Dr. Cohen also expressed the overarching opinion that the scientific community rejects the concept (based on present science) of a link between ASDs and mitochondrial disease (even

[65] While I filed the Haas article as a Court Exhibit, Dr. Cohen also referenced the article extensively in his testimony. *See, e.g.*, Tr. at 431.

though in rare circumstances developmental regression is seen with certain mitochondrial diseases). Tr. at 437. He recalled that when he began studying mitochondrial disease, it was widely theorized that autism might be related, given similarities in how suddenly the symptoms could develop, and/or how they seemed to involve similar energy deficiencies. *Id.* However, as understanding of mitochondrial diseases expanded, in his view medical science was slowly reaching the conclusion that there was no such relationship, given how few of those diagnosed with autism also presented with known symptoms of a mitochondrial disease, and the lack of other links. *Id.* at 438.

Turning to the record herein, Dr. Cohen explained why he differed with Drs. Kendall's and Frye's mitochondrial disease diagnosis. Tr. 455-56. In Dr. Cohen's view, L.V. merited a score of zero on the Morava scale, given the minimal morphologic data, and lack of persuasive enzymology test results. Resp't's Ex. A at 12. Rather, Dr. Cohen asserted that L.V.'s medical history and clinical phenotype reflected autism without a known etiology. Tr. at 440.

In so doing, Dr. Cohen provided his own understanding of the value of the Morava criteria, especially in light of subsequent scientific thinking on the diagnosis of mitochondrial disease. Tr. at 462-63. He pointed out Dr. Kendall's concurrence that Morava had limited application as the most up-to-date criteria (in particular given the availability today of genetic testing), and that the community of mitochondrial disease-oriented specialists were generally "walking away" from its use. *Id.* at 463-64, 551, 567. He reiterated the general point that Morava gives too much weight to nonspecific symptoms (for example, "exercise intolerance"). *Id.* at 445-46. He also stressed, however, that even current clinical diagnostic criteria for evaluating whether a mitochondrial disease was present could not be applied precisely in most cases, and could accordingly result in certain test results being interpreted as abnormal when they did not in fact suggest the presence of disease. *Id.* at 464-65.

Dr. Cohen examined Dr. Frye's specific application of the Morava criteria in detail. Tr. at 440-41, 444. At the outset, Dr. Cohen observed that L.V.'s clinical presenting features (primarily autistic symptoms and developmental regression) were not congruent with the severe disease phenotypes displayed by children in the study used to develop the Morava criteria (such as MELAS or Leigh disease). *Id*. at 465-66, 603. Dr. Cohen therefore suggested that (although he did not take issue with Dr. Frye's decision to consider the possibility that L.V. had a mitochondrial disease), the diagnostic utility of the Morava criteria in this context should have been viewed with some skepticism.

Turning to the specific Morava criteria tallies, Dr. Cohen opined that the point given by both Drs. Kendall and Frye for exercise intolerance was inappropriate. Exercise intolerance seen in relation to a mitochondrial disease is typically a product of "myopathy, muscle disease, or nerve

neuropathy, nerve disease, or cardiomyopathy."[66] Tr. at 445. Here, however, L.V.'s medical history not only was far more vague in depicting L.V.'s purported intolerance, but it was also a far cry from the kind of byproduct symptom commonly seen with true mitochondrial disease. *Id.* at 445-46.

Dr. Cohen also challenged the point denoted by Dr. Frye for L.V.'s ASD. Tr. at 469. In Dr. Cohen's interpretation, L.V's developmental regression was more reflective of idiopathic autism than a mitochondrial disease. *Id.* at 471-72. In patients with mitochondrial diseases, Dr. Cohen testified, problems in brain function are clearly demonstrated through evidence of brain atrophy, lesions in the brain, and/or lactate peaks on their MRI scans, and can result in dementia and other severe, progressive declines in function that are measurable. *Id.* at 575. That kind of drastic loss of cognitive skills associated with mitochondrial diseases is readily distinguishable from the loss of cognitive skills in autism, or the loss demonstrated by L.V.'s history, which Dr. Cohen argued discounted scoring it under Morava's point system. *Id.*

Dr. Cohen further testified that L.V. should receive a score of zero under the Morava criteria for his purported gastrointestinal symptoms. L.V.'s constipation was mild enough to be relieved by miralax, and therefore did not rise to the level of severity commonly associated with mitochondrial diseases. Tr. at 444; Resp't's Ex. A at 12. Dr. Cohen elaborated that the gastrointestinal disturbances common to ASD look markedly different from those experienced by patients with classic mitochondrial phenotypes. Tr. at 438-39. Patients with definite mitochondrial diseases, like MELAS, experience total, severe obstruction that may require exploratory surgery to find the blockage. *Id.* at 442. In contrast, ASD patient constipation is much less severe. *Id.* at 443.

With respect to the results of various lab tests performed on L.V., Dr. Cohen maintained that even though some of the results revealed abnormalities that might merit some consideration under the Morava criteria, they were either uncorroborated by other confirmatory tests or simply overwhelmed by the weight of far more persuasive evidence that in fact L.V. did not have a mitochondrial disease. Tr. at 477.

Thus, Dr. Cohen expressed the view that the results of L.V.'s laboratory tests were also not worthy of any Morava points. Tr. at 446. With respect to the lactic acid measurements, Dr. Cohen stressed that such testing is routinely prone to false elevation because "struggling" can raise the lactic acid (and struggling is far more likely when a biopsy is obtained from a child). *Id.* at 447. Here, Dr. Cohen proposed that the results showing elevated lactate levels were questionable for that very reason. Resp't's Ex. A at 13. Furthermore, Dr. Cohen noted that L.V.'s amino acid testing

[66] Dr. Cohen describes these, moreover, as "objective disorders" that would be readily evident to a treater. Tr. at 445.

and the alanine-to-lysine ratio[67] results – tests well-understood as corroborating an elevated lactate result – were both normal, and therefore undermined the elevated lactate findings. Tr. at 448-49.

As for the abnormal ethylmalonic acid and tricarboxylic acid/Krebs cycle intermediates test results, Dr. Cohen did not consider the results to be sufficiently high, or sufficiently confirmed by additional testing, therefore suggesting only that further in-depth evaluation was required to determine if there was in fact mitochondrial dysfunction. Tr. at 450, 559-60. In addition, the acylglycine test results (used to help confirm the meaningfulness of abnormal ethylmalonic acid and kreb cycle intermediates results) were normal, further diminishing the value of some of these abnormal biomarker test results. *Id.* at 450.

The last category – mitochondrial morphology – also received a score of zero from Dr. Cohen. Resp't's Ex. A at 10, 12. While Dr. Cohen agreed that abnormal morphology – specifically the presence of increased mitochondria with some swelling (Resp't's Ex. A at 7) – was seen on L.V.'s electron microscopy, there were "no light microscopy correlates." *Id*. at 13. According to Dr. Cohen, there are "well-established immunohistochemical features" that should have been seen on "light microscopy," such as ragged red fibers and COX-negative fibers, none of which were found in L.V.'s muscle biopsy. *Id*. Otherwise, the finding that L.V.'s electron miscroscopy results showed swollen mitochondria was more consistent with a lab error than disease, and would therefore "be a stretch" to award a point under Morava. *Id*. at 11; Tr. at. 451-56. If the swelling was in fact indicative of a mitochondrial disease, the patient would also display disruption in the interim crystalline structure. Tr. at 457. Moreover, the amount of cytochrome oxidase enzyme[68] (102 percent), citrate synthase[69] (107 percent), and succinate dehydrogenase[70] (116 percent) present were within normal range, and thus not elevated enough to be of concern. *Id*. at 459.

Dr. Cohen took issue with two of the pieces of literature offered in support of Dr. Kendall's report. He dismissed her reference to the *Poling* article (a case report involving vaccines other than the flu vaccine) as insufficient to draw an association between vaccinations and the development of mitochondrial disorders in children with autism. Tr. at 476-77. He similarly dismissed the

[67] Alanine is a "nonessential amino acid, 2-aminopropanoic acid, occurring in proteins; high levels also occur free in plasma." *Dorland's* at 43. Lysine is an essential amino acid and is "necessary for optimal growth in infants and for maintenance of nitrogen equilibrium in human adults." *Dorland's* at 1089.

[68] Cytochrome oxidase is "an enzyme complex of the inner mitochondrial membrane that catalyzes the transfer of electrons from cytochrome c to oxygen, oxidizing the former and reducing the latter in the final step of the electron transport chain by which oxygen is used for fuel combustion." *Dorland's* at 465.

[69] Citrate Synthase is "an enzyme of the transferase class that catalyzes the condensation of oxaloacetate and the acetyl group of acetyl coenzyme A to form citrate and coenzyme A." *Dorland's* at 366.

[70] Succinate dehydrogenase is "an enzyme of the oxidoreductase class that catalyzes the oxidation of succinate to fumarate, using a variety of hydrogen acceptors." *Dorland's* at 1795.

Shoffner article as having little bearing herein. Even if L.V. had a mitochondrial dysfunction, there is, in Dr. Cohen's opinion, no known association between the flu vaccine and aggravation of a mitochondrial disease. *Id.* at 479-80.

Finally, Dr. Cohen addressed some components of Dr. Shafrir's theory that L.V.'s regression was the result of an autoimmune encephalopathy. He disputed that L.V. had experienced a regressive form of autism caused by an autoimmune encephalopathy induced by the first vaccination and magnified by the second vaccination, observing that the record suggested that L.V.'s problems actually began prior to his first flu vaccination. Tr. at 482-83. Dr. Cohen also challenged the conclusion that L.V. had experienced any traumatic brain injury along the lines of an encephalopathy, noting that MRI scans of children with autoimmune encephalopathy will often show particular abnormalities absent in this case. Thus, testing of brains in cases of anti-NMDA receptor antibody autoimmune encephalopathies will often show disease in the temporal lobes or other parts of the brain. *Id.* at 508-09. But, as conceded by Dr. Shafrir, L.V.'s MRI showed no similar abnormalities. *Id.* at 363. Moreover, none of L.V.'s treaters performed the kinds of tests that Dr. Cohen would expect would be performed if anti-NMDA receptor encephalitis had been suspected (such as a spinal tap, an imaging study like a CT scan or an MRI scan, or an EEG), nor was immunoglobulin therapy[71] effective for L.V. *Id.* at 363, 510-13. L.V.'s change in developmental status was far more gradual and mild overall than indicated by the timeline of regression supported by Petitioners, and therefore not reflective of a dramatic autoimmune reaction. *Id.* at 511, 514.

IV. SUMMARY OF RELEVANT MEDICAL CONCEPTS

Prior to analyzing Petitioners' claims, it would be beneficial to briefly consider the two medical conditions most relevant to this case (along with relevant case law dealing with both in the Vaccine Program): ASDs and mitochondrial disorders. The summary below is derived from materials filed by both parties in this case, as well as discussions of the conditions set forth in the decisions of other special masters or the Court of Federal Claims.

A. Autism Spectrum Disorder

Autism or ASD encompasses a group of complex neurodevelopmental disorders characterized by "self-absorption, impairment in social interaction and communication, and a restricted range of activities and interests." *Dorland's* at 180; *see also* Autism Spectrum Disorder Fact Sheet, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKES, Oct. 7, 2015, *available at* http://www.ninds.nih.gov/disorders/autism/detail_autism.html (last visited Feb. 11,

[71] Immunoglobulin therapy is often used to treat NMDA receptor antibody autoimmune encephalopathy. Tr. at 513.

2016). Children diagnosed with ASD are often reported by their parents to have displayed developmental or behavioral problems around 18 months of age, if not by the age of two, and a significant minority of children with ASD experience regression/loss of skills, including language or vocabulary. *Lehner v. Sec'y of Health & Human Servs.*, No. 08-554V, 2015 WL 5443461, at *34-35 (Fed. Cl. Spec. Mstr. July 22, 2015) (discussing the diagnostic criteria and characteristics of ASDs).[72]

Since the resolution of the OAP cases, there have been numerous petitions attempting to establish that a variety of vaccines cause autism or an ASD, based on causations theories highly similar to those asserted in the present action. *See, e.g.*, *Hardy v. Sec'y of Health & Human Servs.*, No. 08-108V, 2015 WL 7732603, at *4-5 (Fed. Cl. Spec. Mstr. Nov. 3, 2015) (petitioners failed to demonstrate that DTaP vaccine caused or significantly aggravated underlying mitochondrial disease resulting in ASD); *Miller v. Sec'y of Health & Human Servs.*, No. 02-235V, 2015 WL 5456093 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (petitioners failed to demonstrate that several childhood vaccines caused encephalopathy or aggravated underlying mitochondrial disease/dysfunction); *Lehner*, 2015 WL 5443461 (petitioners failed to demonstrate that flu vaccine resulted in autoimmune encephalitis). As Special Master Hastings noted in the recent *Hardy* decision, however, to date *every* post-OAP non-Table claim[73] seeking compensation for autism injuries purportedly related to a vaccine that has been tried has failed. *Hardy*, 2015 WL 7732603, at *4-5 (referencing eleven autism claims unsuccessfully tried (including *Miller* and *Lehner*), plus six that were rejected (over the petitioners' objections) without trial)).

B. Mitochondrial Disease and Diagnostic Criteria

Mitochondrial disease is (as put by Dr. Kendall) a "heterogeneous group of disorders that affect the body's ability to ultimately metabolize energy through a series of complicated reactions

[72] In this case, other than some occasional disagreement about the diagnostic value of the term "regressive autism," the parties did not dispute L.V.'s ASD diagnosis, and therefore offered no medical literature directly defining the term. I reference *Lehner* (which does cite to several exhibits offered therein) and its discussion of ASD's characteristics only for the broad purpose of framing this topic.

[73] In a single instance, petitioners (the parents of a vaccinated child) successfully established a Table injury – an encephalopathy – after vaccination that resulted in 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. Petitioners in this case rely on the same expert, Dr. Shafrir.

inside the mitochondria." Tr. at 112-13. Mitochondrial disease can manifest with a multitude of symptoms, including autism or autistic features and gastrointestinal symptoms, both of which L.V. experienced. *Id.* at 113, 173. Classic phenotypes of mitochondrial disease are "usually progressive and multisystemic" (Haas at 1327) and progressively severe, especially in the case of infants and young children. *Id.* at 1329-30. But (as all experts testifying in this case agreed), 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 1327; Tr. at 114, 431-32. Thus, based upon up-to-date medical and scientific thinking on the topic, the clearest diagnostic evidence that an individual in fact has a mitochondrial disease is provided by genetic testing. Haas at 1327; Tr. at 433-44.

There are differences between a mitochondrial "disease," "disorder," and "dysfunction." As Dr. Kendall put it, "mitochondrial disease is a situation in which either you have definitive information that clearly states that this person has a mitochondrial disease based on laboratory and other factors," while mitochondrial dysfunction is the proper term when there is not a clear diagnosis. Tr. at 115. Dr. Cohen largely echoed this distinction, albeit by reframing the distinction as between primary and secondary mitochondrial disease (which, as Haas defines it, is the result not of a genetic mutation directly affecting the functioning of the electron transport chain, but instead reflects impairment of the oxidative phosphorylation process by an "unrelated genetic or environmental cause.") Haas at 1330; Tr. at 435-36 (characterizing the phrase "mitochondrial dysfunction" as "a very global generic term"). Ultimately, Dr. Kendall used the terms "mitochondrial disease" and "mitochondrial disorder" somewhat interchangeably, while stressing that the existence of a secondary mitochondrial disease, less severe than more classic phenotypes such as Leigh disease, was nevertheless in her opinion sufficient to make the introduction of a vaccine problematic. Tr. at 235.

The Petitioners' argument that L.V. suffered from some form of mitochondrial disease relies on a specific set of diagnostic criteria applicable to children first set forth in 2006 and referred to in this decision as the "Morava" criteria. *See generally* Pet'rs' Ex. 41, Ref. 25. It is uncontested that Dr. Frye's and Dr. Kendall's diagnoses of L.V. rely on application of the Morava criteria. Tr. at 120. Dr. Cohen also applied these criteria in reviewing Petitioners' arguments (although he questioned whether they have become obsolescent in light of scientific progress in understanding mitochondrial disease).

The Morava criteria include three broad categories – clinical signs and symptoms, metabolic/imaging studies, and morphology – and then, within each category, assign points to certain defined symptoms or test results as set forth on a table contained in the article in which the criteria were first proposed. Morava at 1824. Thus, one of the subcategories under the "clinical signs and symptoms" heading is "CNS presentation," which in turn sets forth ten different possible symptoms, such as seizures, developmental delay, or cortical blindness, each of which is worth a point under the proposed Morava system, with a "cap" of two points possible for this category. *Id.*

Similarly, the metabolic/imaging studies category sets forth eleven possible test results that could merit awarding points (such as evidence of ethylmalonic aciduria or elevated lactate). *Id.*

Once points have been assigned, they are totaled and then compared to a range to determine the likelihood that the patient has a mitochondrial disease. A score of one means that disease is unlikely; two to four points merit a determination of "possible" mitochondrial disease; five to seven points suggest mitochondrial disease is "probable"; and eight points or more result in the determination that mitochondrial disease is definitely present. Morava at 1824 (Table). By the Morava criteria's own parameters, some symptoms are given slightly less weight than others, with certain muscle biopsy morphology results given up to four points. *Id.* Indeed, as the Morava authors acknowledged at the time of the article's writing, some of the criteria's utility lay in making the very determination as to whether a muscle biopsy should be performed. *Id.* at 1823 ("[t]he method could also be applied in children with a suspected mitochondrial disorder prior to performing a muscle biopsy").

Importantly, however, in the ten years that have passed since the publication of Morava, there has been refinement of the diagnostic tools used to make the difficult determination of whether an individual in fact suffers from a mitochondrial disease. Haas anticipated this progress,[74] drawing a line between "red-flag" evidence of mitochondrial disease (Haas at 1327 (Table 1)) and "nonspecific" findings that "do not indicate a mitochondrial problem per se, although their presence should prompt concern." *Id.* at 1328 (Table 2). Haas also stresses that genetic testing is the most telling clinical factor, along with the "limited utility" of measuring lactate and/or pyruvate via a muscle biopsy (*id.* at 1329) – a test that had only a few years previously been (Dr. Kendall agreed) the "gold standard" for making the diagnosis. Tr. at 118. Although both mitochondrial disease experts applied the facts to Morava, they largely agreed that the best approach to diagnosing the disease is broader and less rigid than Morava's framework. Tr. at 143, 240 (Dr. Kendall stating that she uses the Morava criteria – albeit "loosely"); *Id*. at 463 (Dr. Cohen agreeing with Dr. Kendall in the imprecise application of Morava).

It has become more common for Vaccine Program petitioners to assert that a particular vaccine caused, or exacerbated, a child's preexisting, often-unidentified metabolic disorder, such as a mitochondrial disease, and that the disease was affected by the vaccine in such a way as to precipitate the child's autism or ASD-like symptoms. However, to date the vast majority of

[74] As previously noted, I filed Haas as a Court Exhibit. Haas has previously been discussed in other cases in which a petitioner sought to establish a causal relationship between a child's receipt of a vaccine and her subsequent ASD, due to a preexisting mitochondrial disease. *See, e.g.*, *Padmanabhan v. Sec'y of Health & Human Servs.*, No. 11-141V, 2015 WL 1736345, at *18 (Fed. Cl. Spec. Mstr. Mar. 26, 2015), *mot. for review den'd*, No. 11-141V (Fed. Cl. Aug. 6, 2015), *aff'd*, ___ F.3d ___, 2016 WL 463085 (Fed. Cir. 2016) (applying Haas (also filed as a court exhibit) in case in which petitioners alleged that child's preexisting mitochondrial disease was aggravated by vaccines, resulting in ASD).

petitioners have failed in establishing any of the *Althen* elements in support of this kind of theory, regardless of the vaccine at issue. *See, e.g.*, *Hardy*, 2015 WL 7732603; *R.K. v. Sec'y of Health & Human Servs*, *slip. op.* (Fed. Cl. Spec. Mstr. Sept. 28, 2015), *mot. for review den'd*, ___ Fed. Cl. __ (Dec. 18, 2015); *Padmanabhan v. Sec'y of Health & Human Servs.*, No. 11-141V, 2015 WL 1736345 (Fed. Cl. Spec. Mstr. Mar. 26, 2015), *mot. for review den'd*, No. 11-141V (Fed. Cl. Aug. 6, 2015), *aff'd*, ___ F.3d ___, 2016 WL 463085 (Fed. Cir. 2016) (petitioners failed to demonstrate plausible causation theory in support of claim that child's preexisting mitochondrial disease was significantly aggravated by vaccines).

The only exception to the above is *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373 (Fed. Cir. 2015). There, the Federal Circuit affirmed a Court of Federal Claims' determination that a special master erred in denying compensation to petitioners claiming (in a non-Table case) that the MMR, varicella, and pneumococcal vaccines significantly aggravated their child's mitochondrial disease, resulting in severe neurodegeneration. However, that case is facially distinguishable – not only because it involved different vaccines and a more obvious immediate reaction[75] to them (that, significantly, was classified as "neurodegenerative," rather than as an ASD), but more importantly because the child's mitochondrial disease was not a contested fact (as is the case here). The result in *Paluck* thus cannot be reasonably understood to predict the theory's likely acceptance in future decisions, but instead was the product of its own unique set of facts. *See, e.g.*, *Hardy*, 2015 WL 7732603, at *35 (Fed. Cl. Spec. Mstr. Nov. 3, 2015) ("in no case presented to me . . . has there been presented any persuasive evidence that even in a child with an actual mitochondrial disorder, vaccines can cause or aggravate that child's ASD").[76]

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[75] The vaccinated child (a one-year old) in *Paluck* had experienced a persistently high fever in the two to seven days immediately after receiving the vaccines, and was soon thereafter diagnosed with possible neurologic problems confirmed by MRI results, among other things. *Paluck*, 786 F.3d at 1376. Also likely relevant to the causation theory offered in *Paluck* was the fact that the *Paluck* petitioners relied on Dr. Frye himself as their testifying expert – unlike here, where Dr. Frye's diagnosis is only indirectly referenced (and not wholly accepted by Dr. Kendall either).

[76] Petitioners have suggested that the Federal Circuit's finding that Respondent "conceded" the causation theory offered in *Paluck* bulwarks the theory's reliability in this case. Petitioners' Post-Trial Brief (ECF No. 155) at 65-66. But it is a well-worn axiom in Vaccine Program cases that the results in one case do not dictate the results in another. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). A corollary principle is that Respondent's concession based on the facts of a particular case similarly does not bind Respondent in a different case. *Padmanabhan*, 2015 WL 1736345, at *42 n.115 ("a concession by respondent in one case does not constitute a concession in another, as science and medicine are not immutable, and evidence filed in one case may not be filed in another case. For example, a concession that the measles vaccine can cause an encephalopathy occurring within five to fifteen days of a vaccination is not a concession that it can do so at times shorter or longer") (*citing Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)). In this case Respondent unequivocally does *not* concede the theory's reliability or plausibility. Respondent's Post-Trial Brief (ECF No. 157) at 21 n.8; Tr. at 477-78, 480, 482.

Moreover, Petitioners exaggerate the extent to which Respondent actually conceded the *Paluck* causation theory. Although Respondent's expert in *Paluck* admitted, during the initial hearing and while under cross-examination, that the theory had plausibility, Respondent never formally agreed that Petitioner had established this particular *Althen*

V. APPLICABLE LEGAL STANDARDS

A. Petitioner's Overall Burden in Vaccine Program Cases

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – i.e., an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[77] No Table claim is asserted in this case, nor do I find the facts would support one.

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

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prong. In addition (as observed by the special master presiding over the case, after it was remanded to him the first time), Respondent effectively dropped the issue entirely (perhaps discouraged from further litigating it after the Court of Federal Claims' first remand, in which the Court strongly indicated its view that the evidence presented was sufficient to satisfy the "can cause" first *Althen* prong). *Paluck v. Sec'y of Health & Human Servs.*, No. 07-889V, 2013 WL 2453747, at *42 (Fed. Cl. Spec. Mstr. May 10, 2013), *mot. for review granted*, 113 Fed. Cl. 210 (2013), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015) (*Paluck* special master noting that even though Respondent had not made an "outright concession" of petitioners' theory, she "did not present any substantive argument regarding prong one of *Althen* in any of her post-remand briefs"). Although an unrebutted evidentiary showing, and/or admission by a witness, may constitute a "concession" within that single case for purposes of determining whether a petitioner has met his "can cause" causation burden, such an occurrence cannot be expanded to mean that the Respondent has accepted the scientific or medical plausibility of the same theory applied to different fact patterns.

[77] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon*, 40 Fed. Cl. at 630. By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

13(a)(1).

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

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, 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." *Knudsen*, 35 F.3d 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 Dep't of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011).

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

In this matter, besides arguing that the flu vaccine caused L.V.'s autism and/or autistic regression, Petitioners also offer a parallel theory that the flu vaccine significantly aggravated a preexisting condition in L.V. – his purported mitochondrial disease. Where a petitioner so alleges, the *Althen* test is expanded, as a petitioner has additional evidentiary burdens to satisfy. *See generally Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (2009). In *Loving*, the Court of Federal Claims combined the *Althen* test with the test from *Whitecotton v. Sec'y of Health & Human Servs.*, 81 F.3d 1099, 1107 (Fed.Cir.1996), which related to on-Table significant aggravation cases. The resultant "significant aggravation" test has six components, which are:

(1) the person's condition prior to administration of the vaccine, (2) the person's current

> condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144; *see also W.C. v. Sec'y of Health & Human Servs*., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims"). In effect, the last three prongs of the *Loving* test correspond to the three *Althen* prongs.

B. Law Governing Analysis of Fact Testimony

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

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr.

Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs*., 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms. It is equally unlikely that pediatric neurologists, who are trained in taking medical histories concerning the onset of neurologically significant symptoms, would consistently but erroneously report the onset of seizures a week after they in fact occurred").

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

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

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v.*

Sec'y Health & Human Servs., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 2014 WL 1258137 (Fed. Cir. Mar. 28, 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 petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743

(quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (*citing Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

In determining whether a particular expert's testimony was reliable or credible, I may consider whether the expert 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) I heard and have considered all of the testimony of the experts offered at the entitlement hearing, I may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See e.g.*, *King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78-79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications). The mere fact that a person dons a "white lab coat," so to speak, and then offers an expert opinion does not imbue that opinion with automatic legitimacy.

VI. ANALYSIS

Both of the Petitioners' causation theories depend on evidentiary fact-findings in their favor – either that L.V. had a specific, preexisting mitochondrial disorder, or that he experienced an autoimmune encephalopathy that in turn produced a dramatic, post-vaccination regression. It is logical to first determine if the evidence supports either requested finding before considering if the *Althen* prongs can be satisfied. *Broekelschen*, 618 F.3d at 1346 (when an injury or diagnosis is disputed, and "the proposed injuries differ significantly in their pathology," the special master may "first find which of [the] diagnoses was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury").

A. L.V. Did Not Have a Mitochondrial Disease or Mitochondrial Dysfunction.

Neither expert accepted Dr. Frye's diagnosis that L.V. had a "definite" mitochondrial disease under the Morava criteria, so the primary fact issue posed at trial was whether the evidence established a "probable" disease. Resolving this issue required weighing the testimony of Dr. Kendall[78] against that of Dr. Cohen, and evaluating their competing interpretations of the various test results relevant to the disputed diagnosis. Although Dr. Cohen has more overall experience in the specialty of mitochondrial disease,[79] both experts were qualified to opine on the topic, and I found both comprehensible in their testimony and willing to concede reasonable points.

Dr. Cohen's opinion, however, in light of the relevant facts gleaned from the medical records as well as its logic, was the more persuasive of the two. In particular (and although Dr. Cohen did directly grapple with Petitioners' argument that L.V.'s test results and other symptoms met the Morava criteria for diagnosis), his underlying point – that the Morava criteria have been supplanted by more precise diagnostic guidelines, and are therefore not a reliable basis for assessing whether a child has a mitochondrial disease – had considerable force and was unrebutted by Petitioners.

As Dr. Cohen established, Morava's point system, despite its seeming structure, is imprecise, giving too much weight to nonspecific findings, such as exercise intolerance or gastrointestinal problems, and equating them with "red flag" evidence that is closely linked with well-recognized phenotypes of mitochondrial diseases. Petitioners have thus relied on an outdated diagnostic toolset, since current science and medical knowledge (which has made more definitive tests like genetic testing possible) has cast doubt on the significance of certain criteria previously considered important. Thus, even if the Morava criteria were correctly applied under the circumstances to reach the *tentative* conclusion that L.V. had some mitochondrial disease (subject to a muscle biopsy – one of the possible uses for the criteria, as the article itself indicates (Morava at 1823)), it is evident today that overreliance upon it is inadvisable.

I therefore do not accept Petitioners' assertions that the determination that L.V. had a mitochondrial disease is simply a matter of deciding if Morava's point system is satisfied by the evidence. Rather, I find persuasive Dr. Cohen's testimony that, based on the more up-to-date

[78] Dr. Kendall adequately explained Petitioners' mitochondrial disease-related causation theory. I therefore do not address Dr. Shafrir's brief parallel statements about mitochondrial disease and its relevance to this case (although I also note that he plainly lacked sufficient professional expertise in the field to reliably comment on it).

[79] Dr. Cohen has the edge over Dr. Kendall in experience studying mitochondrial disease, diagnosing it in patients, and treating it. Indeed, he was an author of Haas, a piece of literature that was especially persuasive in evaluating advances in diagnosing mitochondrial disease. I therefore give more weight to his conclusions simply (although not exclusively) on this basis.

diagnostic guidelines that differentiate nonspecific symptoms[80] from "red flag" symptoms, the overall weight of the evidence – which takes into account L.V.'s history and test results – does not support the conclusion that L.V. had such a disease of any kind. L.V.'s medical history is devoid of the kind of clear symptoms associated with the most severe phenotypes of mitochondrial disease like MELAS or Leigh disease, and the results of his testing that would most persuasively confirm the existence of a mitochondrial disease, like a muscle biopsy or genetic test, were negative for the disease. The biomarker test results were largely inconclusive, with some pointing to a possible problem and some not, thus indicating that positive results are worthy of less weight than the Petitioners urge. Applying up-to-date clinical criteria, Petitioners did not establish by a preponderance that L.V. had a mitochondrial disease.

Regardless of the above, even if I simply apply the Morava criteria mechanically to the various test results and other factors in light of it (but based on each expert's interpretation of those results), I still conclude that the evidence does not preponderate in L.V.'s favor. It is undisputed by both testifying experts that neither genetic testing nor L.V.'s lactate levels were supportive of a mitochondrial disease. *See, e.g.*, tr. at 140. Dr. Cohen also persuasively testified to the diminished value of the nonspecific criteria for which Dr. Frye awarded Morava points, such as L.V.'s ongoing constipation, since they did not amount to the kind of more telling, serious indicia that would suggest to most treaters that an individual actually had a mitochondrial disease. *Id.* at 566-67 ("[c]onstipation is common in autism. The constipation doesn't rise to the level that we see it in mitochondrial disease"). And Dr. Kendall admitted that other nonspecific findings, such as exercise intolerance, that were the basis for Morava points had little support in the medical record. *Id.* at 193-94, 245.

The remaining Morava points awarded by Dr. Kendall are based on a mix of biochemical marker and morphology test results. But, as Dr. Cohen established, those findings were either not supportive of the diagnosis, inconclusive in light of subsequent tests (or a failure to repeat an abnormal finding), or could reasonably be interpreted as normal. Dr. Cohen was steadfast in denying the significance of the morphology findings (as observed in the microscopy evaluations of L.V.'s muscle tissue samples), such as the increased mtDNA (which is not associated with pediatric mitochondrial disease in any event) or swollen mitochondria. Tr. at 555-58. He acknowledged that some other biomarker tests (the urinary tricarboxylic acid and ethymalonic

[80] Dr. Cohen's point about the diminished value of many of the nonspecific factors relied upon by Drs. Frye and Kendall herein, in light of the shift in thinking about the most accurate clinical tests for diagnosing a mitochondrial disease, has particular resonance in the context of deciding a Vaccine Program claim. Morava posits that evidence of developmental delay is itself worthy of a "point" in evaluating the presence of a mitochondrial disease – yet in the context of a Vaccine Program claim, it is highly circular and conclusory to argue that the existence of the claimed illness that a vaccine is alleged to have caused is also proof of causation. Although Morava may have some scientific value, this is a legal proceeding, and it is thus reasonable in this context to view skeptically a diagnostic toolset that imbues such nonspecific evidence with significance.

aciduria findings) produced elevated results, but convincingly testified that they were insufficiently high to warrant any additional points. *Id.* at 559, 563.[81]

Drs. Frye's and Kendall's reliance on L.V.'s ASD and related regression as worthy of a Morava point is especially troubling given the undisputed medical record. Dr. Kendall readily acknowledged that L.V. does not have a primary mitochondrial disease, given the lack of severity of other symptoms. Tr. at 237-38. She also struggled to point to evidence from the same record of any dramatic signs of regression post-vaccination, and could identify little to nothing from L.V.'s earlier medical history that evidenced the condition pre-vaccination. *Id.* at 246-49. And yet, as Dr. Cohen noted, it is only the most severe phenotypes of mitochondrial disease that are associated with the kind of sudden and dramatic decompensations that would establish the existence of the disease. L.V.'s mitochondrial disease was, by contrast, (and as Dr. Kendall admitted), mild – but that cannot be squared with the concept that it nevertheless produced a dramatic change in L.V.

In concluding as I do, I am not attempting to diagnose L.V. myself (an act well outside the purview of my function herein). Rather, I am weighing the sufficiency of the evidence presented from a legal standpoint – and finding that such evidence does not make it "more likely than not" that L.V. suffered from a mitochondrial disease of any kind. I have given consideration to the treatment evidence from Dr. Frye upon which the Petitioners rely. But as noted above, a treater's opinion need not be accepted at face value, but is subject to weighing against the other evidence in the case. *Snyder*, 88 Fed. Cl. at 746 n.67. Dr. Frye's conclusions (which were arrived at four to five years ago, and well after the vaccination event in question) are undermined not merely by Dr. Cohen's more persuasive interpretation of the relevant test results, but also by the fact that *none* of L.V.'s immediate treaters (who were present contemporaneously when L.V.'s developmental regression is alleged to have occurred, and therefore better positioned to observe his symptoms) ever opined that L.V. suffered from a mitochondrial disease or dysfunction, whether before or after he received the flu vaccine. Indeed, Dr. Kelley (to whom the Vs were referred by Dr. Frye) reviewed many of those same test results upon which Dr. Frye based his diagnosis, but offered the conclusion that L.V. likely did not have a mitochondrial disease. Pet'rs' Ex. 26 at 32-33; Tr. at 202-04.

B. L.V. Did Not Experience a Post-Vaccination Encephalopathy.

Petitioners offered a second causation theory in this case: that L.V.'s receipt of the flu vaccine precipitated an encephalopathy that resulted in the regression and other ASD symptoms

[81] Even if I credited these test results and agreed with Drs. Kendall and Frye that they merited any Morava points, I would conclude only that the tally of points is three, which under Morava results in the determination of a "possible" mitochondrial disorder. Morava at 1824 (Table). Given the total lack of other, more telling indicia corroborating the diagnosis (genetic testing, lactate levels, or symptoms associated with known disease phenotypes), and conflicting treatment evidence (as evidenced by the conflicting diagnosis of Dr. Kelley), I would still be unable to conclude that such a showing establishes by preponderant evidence that L.V. had a mitochondrial disease.

he experienced. As discussed below (in the section on the *Althen* prongs), there are strong reasons to find this theory wanting. But independent of the theory's scientific plausibility, the facts from the medical records do not support the conclusion that L.V. *did* experience the encephalopathy necessary under this theory.

The medical records from December 2006 and January 2007 are directly relevant to this part of the Petitioners' case. They plainly demonstrate that on December 13, 2016 – five days after L.V.'s receipt of the second dose of flu vaccine – Mrs. V brought L.V. back to the pediatrician, primarily to treat his ongoing constipation. No mention was made of the second vaccination, let alone any of the kind of symptoms that might be expected if L.V. was suffering a reaction to it (in particular, fever). Pet'rs' Ex. 3 at 134-35. The records from this visit also set forth the fact that he was at that time apparently suffering from an ear infection, but do not note any fever associated with it. *Id.*

Significantly, the December 13th records contain the first obvious reference to any developmental problems (specifically, speech delay), but provide no detail about whether they had just recently been observed (as opposed to something noticed before). Pet'rs' Ex. 3 at 135. But speech delay is not itself congruent with the severe regressive occurrence alleged in this case – especially given the absence of evidence of any other kind of medically-concerning reaction to the vaccine received less than a week earlier, such as a high fever. And the probative value of the timing of this reported speech delay is further diminished by later, particularly persuasive contemporaneous evidence (beginning in January 2007) that the Vs repeatedly told treaters that they had observed the start of L.V.'s developmental plateau or regression before he was 22 months old. *See, e.g.*, Pet'rs' Ex. 13 at 8 and Ex. 5 at 4.

The next most significant contemporaneous records relevant to the encephalopathy-related assertions are from December 22 and 26, 2006. These detail treatment of L.V.'s ongoing ear infection, and establish that (several days after the start of the infection) he did eventually develop a fever over 100 degrees, going as high as 104 degrees. Pet'rs' Ex. 3 at 138-40. However, the fever does not appear to have been persistent, and by December 26, 2006, the records merely note a rash, suggesting that in the ensuing period the fever had resolved. *Id.* at 144. Certainly the records do not reflect L.V.'s hospitalization in this period, or any other truly catastrophic reaction requiring emergency intervention; rather, they establish the Vs' diligence in attending to L.V.'s care over the holidays by reporting his fever and other ear infection symptoms to their primary care pediatrician. And there are no further records of L.V. seeing the pediatrician until several weeks later, in January – by which time the Vs had already begun the process of having L.V. professionally evaluated for his developmental problems. Such evidence does not support the contention that L.V. experienced an encephalopathy.

For purposes of comparison, it is instructive to consider the facts of the *Poling* and *Wright*

cases, where petitioners successfully established (or settled) Table claim[82] encephalopathies resulting in ASD symptoms. In the *Poling* case, for example – a matter that the Petitioners have repeatedly argued is highly relevant – the child in question (who was later diagnosed with mitochondrial disease) had received several vaccinations (not including the flu vaccine), and then within 48 hours developed a high fever that became low-grade over the next several days, along with inconsolable crying, sleeplessness, and significant, noticeable motor problems that worsened over the next several days. Pet'rs' Ex. 41, ref. 26 at 170. In *Wright*, the petitioners' child received Pentacel (a multi-virus vaccine)[83], and then, on the drive home from the pediatric visit at which the vaccination was administered, experienced a brief seizure, followed by a week in which he displayed a noticeable decreased level of consciousness and lethargy, during which the child's parents made many unsuccessful efforts to convince the relevant pediatric treaters of the severity of his condition. *Wright*, 2015 WL 6665600, at *12-16. Although both cases are distinguishable for many reasons, together they demonstrate the extreme factual circumstances reflecting an encephalopathy – in contrast to the evidence here.

Petitioners have offered little else to prove that an encephalopathy in fact occurred. An encephalopathy can often be corroborated after the fact, through an MRI, direct evidence of inflammation, or testing demonstrating the presence of certain antibodies associated with autoimmune reactions affecting the brain – but as both of Petitioners' experts admitted, there is no such evidence in this case. Tr. at 201-02, 362-64. And no treaters who saw L.V. at the relevant time opined otherwise. The overall factual record (as Dr. Cohen proposed, based on his review of L.V.'s treatment history and in light of his experience as a pediatric neurologist) does not support the conclusion that L.V. experienced any encephalopathy of the sort that would prompt the dramatic regression alleged by Petitioners. *Id.* at 508-14.

C. Petitioners Have Not Satisfied the *Althen* Prongs.

Petitioners' claim depends upon my finding that L.V. either had a mitochondrial disease or experienced a post-vaccination encephalopathic regression, so my contrary factual conclusions are fatal to their case. Yet review of the three *Althen* prongs for establishing a non-Table causation case reveals that Petitioners could not otherwise prevail on their claim due to evidentiary failures independent of my fact-findings set forth above.[84]

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[82] This case does not involve a Table claim, but *Wright* and *Poling* provide the only comparable instances in which a petitioner has established the kind of encephalopathy that produced the sort of neurologic and/or developmental changes that Petitioners alleged herein occurred to L.V.

[83] Pentacel is the trade name for a vaccine that consists of combined DTaP, inactivated polio virus, and Haemophilus influenza type B vaccines. *Dorland's* at 1406.

[84] Because I have determined that Petitioners have not established by preponderant evidence that L.V. suffered from any form of mitochondrial disease, L.V. also cannot be said to have suffered from a preexisting condition subject to aggravation, and therefore I do not review the first three prongs of the *Loving* test. *See, e.g.*, *Bushnell v. Sec'y of Health*

1. The Flu Vaccine did not Cause L.V.'s Regression (*Althen* Prong Two)

The greatest deficiency in the Petitioners' case is that they have not established by preponderant evidence that the flu vaccine did in fact cause L.V.'s regression – whether directly (by precipitating an encephalopathy that then resulted in a dramatic developmental regression) or indirectly (by impacting L.V.'s preexisting mitochondrial disease, which in turn precipitated the purported regression). Rather, the overall record suggests that any loss of skills or language L.V. suffered likely began before his receipt of the second flu vaccine. The records otherwise do not reveal a dramatic drop-off in skills after the December 8th vaccination, let alone an encephalopathic incident of sufficient magnitude to produce regression.

I find especially probative the numerous occasions on which the Vs reported to ASD specialist treaters that they were aware of L.V.'s problems at 16-18 months, well before he received even the first flu vaccine. The presumption of the accuracy of statements contained in contemporaneous medical records is based on the reasonable belief that individuals attempt to tell treaters as much of the truth about an illness as they can, in the expectation that doing so increases the likelihood of effective treatment. *Capizzano*, 440 F.3d at 1326; *Sanchez*, 2013 WL 1880825, at *2. It is proper to give such records more weight than subsequent testimony attempting to rebut the statements that is otherwise not sufficiently compelling. *Cucuras*, 993 F.2d at 1528; *Sanchez*, 2013 WL 1880825, at *3.

Admittedly, L.V.'s pediatric records before November 2006 say little about developmental problems, as the Petitioners stress. Petitioners have also identified occasional inconsistencies between those records and subsequent autism/developmental evaluation records.[85] But there are

& Human Servs., No. 02-1648V, 2015 WL 4099824, at *19 n.22 (Fed. Cl. Spec. Mstr. June 12, 2015) (no need to apply *Loving* factors to claim that child's autism was significantly aggravated by preexisting mitochondrial disorder where petitioners could not demonstrate any vaccine involvement in child's condition).

Petitioners' significant aggravation theory would, however, still founder on the third *Loving* prong even had they established that L.V. suffered from the milder form of mitochondrial disease proposed by Dr. Kendall. The Petitioners and their experts offered little reliable or persuasive evidence that L.V.'s post-vaccine developmental and behavioral changes were more severe than what a similarly-situated child would experience without vaccination. Indeed – the Petitioners point to L.V.'s ASD symptoms (under Morava) as evidence of his mitochondrial disease, based upon Morava's assumption that developmental problems are associated with mitochondrial dysfunction (even in the absence of vaccination). But if so, this renders it difficult to determine whether L.V. was really worse off post-vaccination than he would have been otherwise, and Petitioners' conclusory argument that this was nevertheless the case is inadequate to establish preponderant proof of this third *Loving* factor. *See Broussard-Pacot v. Sec'y of Health & Human Servs.*, No. 09-107V, 2012 WL 5357478, at *19 (Fed. Cl. Spec. Mstr. Sept. 4, 2012) (petitioners' claim of significant aggravation of preexisting seizure disorder was inadequately "developed or substantiated," because it lacked medical support that child's development would have been different but for the vaccines).

[85] During the entitlement hearing, the Petitioners devoted some effort to suggesting that statements of the Vs from 2007 and later about the onset of L.V.'s regression should be ignored because they were contained in untrustworthy

sufficient documented instances in which the Petitioners made post-vaccination contemporaneous statements about the timing of L.V.'s developmental regression to find that the evidence preponderates against the fact-finding urged by Petitioners. Indeed – Mrs. V admitted to having had concerns about L.V.'s development prior to his receipt of the flu vaccine (a fact Dr. Shafrir also admitted), and thus her testimony was inconsistent in supporting Petitioners' overall claim that the records setting forth the pre-vaccination onset were not credible.

In addition, as discussed above, the evidence pertaining directly to L.V.'s post-vaccination health and developmental condition similarly does not suggest that he experienced an immediate, dramatic change that was vaccine-related, even if some of his developmental problems became more evident after December 8th. The weight of the evidence does not support the conclusion that the second dose of the flu vaccine caused L.V. to react in the manner that the literature suggests a person experiencing an immune-mediated encephalopathic event would, and that could in turn precipitate developmental regression. No evidence was offered to suggest that the flu vaccine was causally related to L.V.'s ear infection, or that the infection was not the source of the fever he subsequently experienced. L.V.'s most immediate post-vaccination illness was constipation (something he had suffered from previously), followed by an ear infection that did not result in fever until almost two weeks after the second flu vaccine dose, and which was successfully treated without hospitalization. The medical records do not corroborate Petitioners' allegations that L.V. experienced an autoimmune reaction from the flu vaccine – as Petitioners' experts admitted. Tr. at 362 (Dr. Shafrir admitting on cross-examination as to the absence of "objective evidence in the record of an immune reaction in L.V.'s brain to the flu vaccine").

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medical records, which were either poor examples of record-keeping, reflected incompetency on the part of the medical professional responsible for creating them, or were contradicted by other documents. Thus, for example, they took particular issue with the statement in Dr. Coplan's January 23, 2007 written assessment that L.V. had only recently begun scoop-feeding ("typically a 12-month milestone," as Dr. Coplan put it (Pet'rs' Ex. 5 at 3)), observing that a September 8, 2006, pediatric record (when L.V. was 18 months old) not only stated that L.V. was "developmentally appropriate" at the time, but also that he "uses spoon and cup." Pet'rs' Ex. 3 at 122-23; Tr. at 539-41. Although I agree the earlier record is inconsistent, I do not find that inconsistency a sufficient basis to discredit Dr. Coplan's entire record (given the number of other subsequent records in which the Vs placed onset before vaccination). It is also reasonable to expect that a pediatric well-child visit would less likely include a careful evaluation of a child's development unless the parents raised the issue (and in fact, when the Vs did raise such issues, they are reflected in such pediatric records), or something obvious occurred during the visit.

There is other evidence, moreover, suggesting that Dr. Coplan's January 2007 assessment about L.V.'s self-feeding capabilities was closer to the truth than the September 2006 pediatric record. Thus, in the January 17, 2007, early intervention assessment performed by Montgomery County (before the Vs informed Dr. Corcoran of their intent to seek early intervention for L.V. and were referred to Dr. Coplan), in the section entitled "Adaptive Development," which asks for a statement on the assessed child's "self-help skills such as feeding," the treater (Dr. Beth Appelbaum) recorded the Vs' statement to her that L.V. "will bring a spoonful of food to his mouth *once Mom has scooped the food*." Pet'rs' Ex. 13 at 7 (emphasis added). This statement (which permits the inference that L.V.'s feeding skills were in fact developmentally behind) is consistent with Dr. Coplan's similar statement.

This is far from a case in which a sudden, dramatic developmental regression is evident – or where a vaccine has a demonstrable, severe physiological effect on an individual which in turn could theoretically be connected to the subsequent regression into an ASD. Instead, the facts are consistent with a more typical ASD presentation – when, over time, parents become aware that a variety of smaller developmental missteps, setbacks, or plateaus in their child's development have significance.

2. Petitioners did not Establish Reliable Causation Theories (*Althen* Prong One)[86]

Neither theory proposed by Petitioners was sufficiently grounded in relevant science to constitute a reliable theory in satisfaction of the first *Althen* prong.

a. *Mitochondrial Disease Theory* - The primary causation theory offered in the case was that a child suffering from a preexisting mitochondrial disease could experience a reaction to the flu vaccine sufficient to produce autism. But the expert responsible for presenting the theory, Dr. Kendall, is not an immunologist. In fact, she was notably circumspect in articulating the components of the theory involving the flu vaccine's "but for" capabilities, preferring instead to emphasize her opinion that the record supported L.V.'s diagnosis of mitochondrial disease. Otherwise, beyond her conclusory suggestion that a vaccine could cause sufficient oxidative stress to an individual with a mitochondrial disease to precipitate a regression, she offered little reliable evidence – whether from her own experience or research, or a laboratory test or case study cited in her report – establishing that the flu vaccine could be so associated with causing developmental regression in children who also suffer from a mitochondrial disease. Tr. at 212-13, 162-63.[87]

Instead, Dr. Kendall's testimony on the flu vaccine's causation role primarily relied on case studies (one of which was merely a description of the facts from *Poling*) that are limited in probative value since they describe only unrepresentative outlier instances that ultimately assume, without direct study or evidence, that vaccination could precipitate a chain of events resulting in

[86] I reject Petitioners' oft-repeated argument in this case that Respondent has waived objecting to their causation theory that vaccines can exacerbate preexisting mitochondrial disorders resulting in autism. As I ruled previously in this matter, the fact that Respondent settled the *Poling* case has no preclusive effect herein, mainly because *Poling* involved a Table claim that was not adjudicated to a reasoned decision. *See* ECF No. 124. Former Chief Special Master Vowell ruled similarly in the recent case of *R.K.,* and the Court of Federal Claims upheld that aspect of her decision (in addition to her bases for denying compensation). *R.K.*, ___ Fed. Cl. __, at 18 (Dec. 18, 2015). Because *R.K.* is subject to a broad redaction challenge (in which the case's index number has been requested redacted), and because the decision is not yet published, my reference to it is vague by necessity.

[87] In addition, Dr. Kendall would not affirmatively state it was "more likely than not" that the flu vaccine had anything to do with L.V.'s condition if in fact his developmental problems preceded the time of vaccination. Tr. at 185-86.

regression. The Shoffner article, for example, involved a retrospective chart review of 28 individuals diagnosed with both mitochondrial disease and an 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 fevers' extent and duration were unknown, as the study relied wholly on parental reports of fever rather than clinically-confirmed data, making that variable unreliable scientifically). But as noted above, the applicability of a study involving high fever as the immediate proximate factor in causing regression is greatly diminished in a case in which evidence of a similarly prolonged, medically-concerning fever is lacking. Nor did Dr. Kendall link Shoffner's findings to additional literature suggesting *any* vaccine's propensity to cause the kind of fever necessary to precipitate the decompensation observed in Shoffner. Indeed – the article's 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"). Such literature may suggest to a scientist an avenue for further study but does not substantiate Petitioners' causation theory.

Thus, Dr. Kendall generally failed to provide reliable evidence plausibly linking the flu vaccine to regression in individuals with mitochondrial diseases. Petitioners offered no other testimony from a qualified immunologist on the topic (the kind of expert best suited to opining on the biologic capabilities or functioning of a vaccine generally).[88]

Petitioners attempted to fill this evidentiary hole with literature – voluminous amounts, much of which was only glancingly referenced during the hearing. *See generally* Pet'rs' Exs. 101-05 and 113-16; Tr. at 153-68. Dr. Kendall was asked at certain points in her testimony to comment

[88] Petitioners attempted to suggest that Dr. Cohen had in the past admitted that vaccines might have some precipitating effect on children with mitochondrial disease, primarily by cross-examining him about an article from 2008 that he co-authored (with nine other specialists), J.R. Weissman, et al*., Mitochondrial Disease in Autism Spectrum Disorder Patients: a Cohort Analysis*, 3(11) PLOS ONE 1-6 (2008) [hereinafter, Weissman]; Tr. at 584-90. Weissman is a retrospective review of the medical histories of 25 ASD-diagnosed patients who also had identifiable mitochondrial disease or dysfunction, and argues that "defective mitochondrial oxidative phosphorylation is an additional pathogenic basis for a subset of individuals with autism." Weissman at 5. Dr. Cohen acknowledged his role in the paper's writing, but testified that before its publication, he tried unsuccessfully to have his name removed as an author. Tr. at 586. He also disputed the accuracy of certain statements it contains, including one proposing that the stress caused by a vaccine reaction might be comparable to that of the "diseases which are known precipitants of mitochondrial regression." Weissman at 4; Tr. at 588. I do not find that Dr. Cohen's prior scientific interest in the possibility of a relationship between a vaccine and regression in individuals with confirmed mitochondrial disease undermines his present testimony that he no longer believes such a relationship exists.

These purportedly inconsistent views of Dr. Cohen (to the extent they are considered his actual views, rather than statements in an article he now claims to have disavowed at time of publication) must also be considered in light of his other, unrebutted testimony that earlier in his study of mitochondrial diseases, he had considered the possibility of a relationship between autism and such diseases, but later rejected the connection. Tr. at 438-39. This, plus the fact that Weissman was written approximately eight years ago, greatly diminishes the significance of Petitioners' suggestion that Dr. Cohen has conceded that a vaccine could have any causal role in precipitating regression or other ASD-like behavioral or developmental problems in children with mitochondrial diseases.

on some of this additional literature. However, in some cases, she was unfamiliar with the cited article (tr. at 164), whereas in other cases she did nothing more than repeat the article's findings and then attempt to relate them to her opinion, rather than demonstrate how her opinion actually arose from or relied upon their findings.[89]

Such literature formed a patchwork theory, attempting to analogize disparate circumstances to the present. At best, some of the medical/scientific evidence offered in this case suggests that children suffering from the most severe phenotypes of mitochondrial disease (e.g., Leigh disease or MELAS) might experience a dramatic regression in development, as one facet of a progressively worsening condition that could result in death, but without any relationship to vaccination. Tr. at 601-04. L.V.'s condition, by contrast, while surely lamentable, is unquestionably not characterized by that degree of severity, as Dr. Kendall acknowledged. *Id.* at 237. There was also evidence offered suggesting that many individuals with ASDs also experience mitochondrial diseases or lesser dysfunction. In contrast, Dr. Cohen forcefully testified that the notion that there is a possible pathogenic relationship between autism and mitochondrial disease has (at least to date) not been sufficiently substantiated by science (and which he personally doubts based on his own experience). *Id.* at 437-39. At bottom, Petitioners failed to offer a reliable theory that such individuals would ever experience a dramatic developmental regression of the kind alleged to have happened to L.V. as a result of the flu vaccine's effects on the body.

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[89] Such articles, moreover, were not especially helpful or pertinent, and reflected the same "connect the dots" approach (linking literature that only facially relates to the causation theories presented in this case, while omitting crucial evidence required for the theory's overall validity) that was so characteristic of Dr. Shafrir's testimony. Thus, for example, Dr. Kendall was asked about Tran. Tr. at 162. Tran involves an in vitro study of the live flu virus (rather than vaccine) and its capacity to induce apoptosis (cell death) in the process of the virus's replication through "dysregulation of the mitochondrial outer membrane permeabilization and the subsequent release of apoptogenic factors." Tran at 1050. Tran has nothing to do with mitochondrial disease or dysfunction per se or a vaccine's capacity to trigger a reaction in an individual suffering from such a disease, however, as its authors explicitly state ("[o]ur study presents evidence to further emphasize the importance of understanding the intricate relationship apoptosis has in promoting influenza virus propagation"). *Id*. at 1059-60.

In the same vein, the Petitioners briefly questioned Dr. Kendall about another article (Pet'rs' Ex. 114, N. Klein, et al., 12 *Evaluation of Immunization Rates and Safety Among Children with Inborn Errors of Metabolism*, PEDIATRICS 1139-46 (2011) [hereinafter, Klein]) ostensibly supporting the proposition that "stressors" could precipitate illness in children suffering from mitochondrial diseases. Tr. at 159-60. Klein presented a retrospective epidemiologic study of a population of immunized children, including a small percentage known to have inborn errors of metabolism ("IEM"). But the article merely concluded that although "the most vulnerable" children demonstrated increased hospitalization rates two weeks after vaccination, "vaccinating children with IEMs with routinely recommended vaccines does not seem to put them at increased risk of adverse effects." Klein at 1146. Citing such an article as support for the notion that the flu vaccine *in this case* could have plausibly harmed a child in L.V.'s circumstances (because it is always possible even if the vaccine in most cases is not contraindicated for children with metabolic disorders, such as a mitochondrial disease) is no more helpful to the Petitioners' case than citing the broadly true, but (from an evidentiary standpoint) irrelevant, fact that the Vaccine Program itself often awards compensation to injured parties even though the relevant vaccine is safe for the vast majority of individuals.

b. *Autoimmune Encephalopathy Theory* - Petitioners' second causation theory – that the flu vaccine can precipitate an autoimmune encephalopathy resulting in regression – is similarly weak.[90] Admittedly, isolated subcomponents of Dr. Shafrir's theory have found acceptance in other Vaccine Program cases, such as the concept of molecular mimicry as the proposed mechanism by which an autoimmune process can occur.[91] But the same cannot be said for his causation theory as a whole. Rather, primary links in the theory chain were missing or proved unreliable, given the disconnect between the theoretical proposition and the evidence offered to support it. As another special master noted in considering the *Althen* prong one analysis, "[t]he weight to be given an expert's opinion is based in part on the size of the gap between the science and the opinion proffered." *Isaac*, 2012 WL 3609993, at *17 (citing *Cedillo*, 617 F.3d at 1339). That gap is far too wide here.

Petitioners could not offer direct evidentiary support establishing the flu vaccine's capacity to function as alleged, in this or other analogous circumstances. Instead, they sought to prove their theory with even more attenuated circumstantial evidence, pointing to studies involving the impact

[90] Dr. Shafrir also posited that L.V.'s purported "immune abnormalities" played a role in his purported reaction to the second flu vaccine dose (tr. at 286-88), but the argument was based on supposition about L.V.'s condition that was not verified by evidence or the overall record, consisting instead of selectively-identified facts (such as L.V.'s allergies). *Id.* at 286. He also proposed Lapphra – a case study involving a single occurrence and a different illness entirely (ADEM) – as suggesting the fact that a second dose of a vaccine could precipitate a neurologic condition, but its fit to the present circumstances was lacking. He later somewhat contradicted this point by admitting that he lacked the evidence, such as genetic proof, for a genetic component to L.V.'s purported "susceptibility" to vaccines. *Id*. at 296.

[91] Although Vaccine Program petitioners are not required to establish a precise biologic mechanism by which a vaccine would have the physiologic effect it is alleged to have, Petitioners herein proposed that the flu vaccine could produce an autoimmune reaction as the starting point of an encephalopathy via molecular mimicry, supporting the contention with seven articles discussing the homologies observed between components of the flu vaccine or virus and different human tissue protein sequences. Tr. at 285, 297-302, 405-06. Molecular mimicry has been found (albeit when applied to different illnesses and diseases) to be a plausible component of a causation theory, as the concept has reliable and reasonable scientific support. *See, e.g.*, *Tompkins v. Sec'y of Health & Human Servs.*, No. 10-261V, 2013 WL 3498652, at *22 (Fed. Cl. Spec. Mstr. June 21, 2013) (in the specific context of establishing causation of Guillain-Barré syndrome occurring after vaccination, "[t]he molecular mimicry theory is the one most widely accepted for the agents most frequently accepted as causal"), *mot. for review den'd*, 117 Fed. Cl. 713 (2014).

In acknowledging the above, however, I do not mean to suggest that molecular mimicry is *always* viewed as a plausible theory in every case. The acceptance of a theory in a single case, or even when commonly invoked to a specific kind of injury, does not mean that the theory can always be offered in rote fashion in other cases and deemed to satisfy the first *Althen* prong. *Hennessey v. Sec'y of Health & Human Servs*., 91 Fed. Cl. 126, 134-35 (2010) (expert's overly broad application of the molecular mimicry theory made it meaningless). For example, an expert unqualified to opine on the topic of molecular mimicry might well be unsuccessful in persuasively offering it as a part of a causation theory. In this regard, I note that Dr. Shafrir lacks the scientific background and experience necessary to persuasively explain molecular mimicry generally, and therefore also is not qualified to apply it specifically to the flu vaccine formulation in question.

of different vaccines, or different formulations of the flu vaccine not used in the U.S., such as Pandemrix. Tr. at 288-92, 363-71, 373-81. They also invoked studies and literature involving brain-centered injuries (as the brain is the likely locus of where a neurologic change resulting in regression would occur) resulting from autoimmune diseases that L.V. unquestionably did not have, such as anti-NMDA encephalitis or other neurodegenerative conditions. Such conditions, more often than not, had been induced by wild virus infections (which were not established by the Petitioners to be comparable in impact to a vaccine simply because they contain the same viral protein chains). Petitioners otherwise invoked individual case studies (*Poling*, for example, or the incident discussed in Lapphra) that are facially distinguishable and otherwise not particularly reliable evidence.

As noted above, Vaccine Program petitioners are not required to prove their causation theories to a degree of scientific certainty, nor must they offer a particular kind of evidence (such as epidemiologic studies). But that does not relieve Petitioners of the obligation to offer proof of their theory that corresponds to facts of their claim. *Moberly*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (a petitioner must "provide a reputable medical or scientific *explanation that pertains specifically to the petitioner's case*" (emphasis added)). Petitioners here have instead offered a strung-together chain of a few individual patient case reports (which "are not, in general, strong evidence of causation" (*Raymo v. Sec'y of Health & Human Servs*., No. 11-0654V, 2014 WL 1092274, at *21 (Fed. Cl. Spec. Mstr. Feb. 24, 2014)), along with scientific or medical articles that themselves do not stand for the principle for which they are cited or are factually inapposite. Similarly, their autoimmune encephalopathy theory makes analogies to different illnesses or vaccines, but without literature or scientific support for the validity of those analogies.

A qualified expert could conceivably tie together such diffuse scientific and medical literature through the force and persuasiveness of his testimony and explanations. Dr. Shafrir is not that expert. He is not an immunologist, does not specialize in the study of autoimmune diseases let alone degenerative encephalopathies precipitated by autoimmunity, is not notably experienced in treating autoimmune-mediated illness, and has no background studying the effect of vaccines on individuals (other than the experience he may have gained either treating patients who he believes were so affected, or through his participation as an expert witness in other Program cases). His broad, multidisciplinary testimony required him to step well outside the bounds of his actual expertise. Although I have nevertheless considered his testimony carefully, it is reasonable to afford it significantly less weight under such circumstances. *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) ("[o]ne very significant fact to consider is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying").

My reaction to the overall ineffective and unpersuasive nature of this second causation

theory should also be placed in context of other Vaccine Program cases in which the same theory was advanced. Dr. Shafrir has asserted a similar causation theory in other cases involving claims about vaccines and autism. *See, e.g.*, *Lehner*, 2015 WL 5443461. In fact, he relied on much of the same literature in *Lehner* as he does in the present case, particularly in discussing molecular mimicry and anti-NMDA encephalitis, and its relationship to developmental or neurologic regression. *Id.* at *47-48. Former Chief Special Master Vowell concluded in *Lehner*, however, that "[t]his evidence fails to demonstrate that Dr. Shafrir's theory has sufficient indicia of reliability to be persuasive," and therefore "Dr. Shafrir's opinions are wishful thinking premised on unverified and unsupported assumptions." *Id*. at *45-47. Based upon my review of the record, and having heard Dr. Shafrir testify in this case, I concur with such statements entirely.

3. Petitioners Did Not Establish a Medically Reasonable Timeframe.

As noted above, the facts support the conclusion that L.V.'s developmental problems were more likely than not evident before he received the second flu vaccine, given the numerous instances in which the Vs so told various ASD specialists. It is reasonable to infer that the Vs would not have repeatedly done so in error. *Cucuras*, 26 Cl. Ct. at 543. In addition, the Petitioners and their experts have acknowledged that the Vs perceived developmental problems in L.V. earlier than December 8th, and their efforts at hearing to distinguish between pre- and post-vaccination problems as qualitatively different were not successful. There is also little to no evidence of any identifiable reaction to the second flu dose, or evidence that it synergistically reacted with L.V.'s ear infection. Finally Petitioners' experts did not offer persuasive causation theories, thus dooming their ability to place onset within the context of those theories.[92]

CONCLUSION

I have great sympathy for the Vs and the suffering they have experienced in their loving care of L.V., and I do not question their sincerity in proceeding with this claim. But the factual record does not support their contention that L.V. suffered from a mitochondrial disease or

[92] Dr. Kendall was for her part able to cite only one piece of literature, Edmonds, suggesting what the timeframe would be (3-7 days) for the flu vaccine to theoretically have had the alleged effect on an individual with a preexisting mitochondrial disease. Tr. at 166. That piece of literature has been found to be reliable in other circumstances (most notably the *Paluck* case). *Paluck v. Sec'y of Health & Human Servs*., 104 Fed. Cl. 457, 481-82 (2012). But the "fit" of medical or scientific evidence offered in support of a theoretical component of a theory to the facts of an action is relevant in weighing its probative value. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 591-92 (1993). Edmonds (like many other articles cited in this matter) involved the result of infection by wild-type viruses rather than vaccination (which cannot be presumed to have the same effect biologically). Tr. at 167 (*citing* Edmonds at 360). Petitioners did not otherwise establish (beyond their experts' *ipse dixit*) that the flu vaccine would have the same effect, or in the same amount of time.

experienced an autoimmune encephalopathy, that the flu vaccine had a causal connection to L.V.'s developmental regression and subsequent ASD diagnosis, or that the vaccine *could* produce the kind of regression or ASD symptoms L.V. experienced. The desire to find some explanation for L.V.'s condition is understandable – but the arguments presented herein purporting to provide that explanation are not enough to meet the standards for an entitlement award in the Vaccine Program.

I therefore DENY an entitlement award in this case. I instruct the Clerk of Court to enter judgment dismissing the case unless a motion for review is filed.[93]

IT IS SO ORDERED.

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

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